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The American Heart Journal

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The American Heart Journal

VOL. III OCTOBER, 1927 No. 1

Original Communications

ANGINA PECTORIS IN YOUNG PEOPLE*

PAUL D. WHITE, M.D., AND SEELEY G. MUDD, M.D.
BOSTON, MASS.

INTRODUCTION

ANGINA pectoris may occur in young people less than thirty years of age. Until we had ourselves encountered such individuals we had remained somewhat skeptical of the cases reported in the literature. The present paper has resulted from our observation of six such persons during the past two years: three patients seen in private and three in hospital practice. A search of the records of the Massachusetts General Hospital has brought to light two more cases: one in 1901 and one in 1913. These eight patients will be described presently and a brief review of the literature given.

After the age of thirty years angina pectoris becomes progressively more common, although it happens that among private patients seen by us, and in a survey of the hospital records here, only seven cases were found between the ages of thirty and forty years—four private and three hospital patients. Of 303 cases of angina pectoris seen by one of us in private practice in the past six years there were 7, or 2.3 per cent, under the age of forty, 4 with onset between thirty and forty years, 1 with onset between twenty and thirty, and 2 under twenty years (sixteen and eighteen years old respectively).

The patients to be discussed all showed definite angina pectoris, consisting of attacks of substernal oppression, usually radiating to the left arm and disappearing on rest or by the use of nitroglycerin in particular. Heart ache or pain associated with effort syndrome, nervous fatigue, mitral stenosis, acute pericarditis, paroxysmal tachycardia, or congestive failure has been carefully excluded. The fact that a person with angina pectoris is young and may have a good prognosis does not warrant the use of misleading terms, such as sec-

*Presented at Massachusetts General Hospital, Boston, January 13, 1927.

ondary or pseudoangina. Angina pectoris is a symptom, representing a clinical entity, and as such is either present or absent. Rare doubtful cases however do occur.

REVIEW OF THE LITERATURE

Heberden himself, in his original study of angina pectoris 150 years ago, found in a group of almost 100 cases one youth, a boy of twelve years, with the condition. Since that time others, among them Osler and Mackenzie in particular, have reported that they have encountered young people with angina pectoris. Osler cites more of such cases than any other writer. In a series of 268 patients he reports 41 between the ages of thirty and forty years and 9 under the age of thirty. Mackenzie does not give the ages at onset of all of the 380 cases about whom he had completed notes, but in the detailed reports of 160 cases published in his book on *Angina Pectoris* there are 3 cases under the age of thirty years and 14 more between thirty and forty years old. A few other cases have been ruled out because the heart pain or distress was not definite angina pectoris. Mackenzie's 3 patients who had angina pectoris beginning under the age of thirty years all had the "rheumatic" type of heart disease. The first (Case 83) was a woman of twenty-five years with aortic regurgitation who continued for eighteen years unchanged up to the last report by Mackenzie when she was still having frequent attacks of angina pectoris at the age of forty-three years; the second (Case 92) was a lad of seventeen years with aortic regurgitation who lived for twenty-five years longer with angina pectoris; and the last (Case 113) was a boy with adhesive pericarditis and probable mitral disease with angina pectoris who was observed from the beginning of his illness at the age of seven until his death at fourteen years of age.

In a series of 200 cases of angina pectoris, Herrick and Nuzum recorded 2 as between twenty and thirty years old, and 14 others between thirty and forty years old. Philips in his series of 179 cases of angina pectoris reported 2 between the ages of twenty and thirty years, and 5 between thirty and forty. Schmidt in 121 cases found 2 patients between twenty and thirty years of age and 11 between thirty and forty. Levine in a group of 103 cases cited 2 patients with rheumatic aortic insufficiency, aged nineteen and twenty-nine years respectively; one of these showed also aortic stenosis. Gallavardin in 100 cases found only 4 below the age of forty years. Syllaba reported that of 100 cases, 15 were from thirty to forty years old, mostly luetic, with ten deaths within a few years. Kahn in 82 personal cases found 19 (24 per cent) between the ages of thirty and forty years, but none under thirty. Kilgore has cited 2 cases of angina pectoris between thirty and forty years of age in his series of 36 individuals, but none under thirty. Houchard quoted Gauthier's report of 4 individuals

with angina pectoris between the ages of ten and twenty years. Telia cited 3 cases of angina pectoris with rheumatic mitral stenosis aged seventeen, eighteen, and twenty-seven years respectively. Vaquez in his book on heart disease noted the sudden death of a lad of eighteen years who showed at postmortem examination aortitis and marked narrowing of both coronary arteries. Gibson referred in his book on heart disease to two youthful cases of angina pectoris; one a patient aged twenty-four years reported by Balfour, and another aged twelve years with sudden death and coronary sclerosis, cited by Wild. Hirschfelder has noted the case of a boy eight years old with mitral stenosis and angina pectoris. Trousseau diagnosed angina pectoris in a man of twenty-five years and stated that Desportes in 1811 described a case of Fothergill's, a young man thirty years old with the same complaint. Rutherford reported the case of a child six years old with angina pectoris and pericarditis. Moon cited the record and postmortem examination of a young woman nineteen years old who had aortic regurgitation and mitral valve disease with angina pectoris. Gilford, in 1904, described with postmortem examination a prematurely senile dwarf who died of angina pectoris at the age of eighteen years. He showed extensive arteriosclerosis of the aorta and coronary arteries. Anstie reported angina pectoris in a boy with aortic stenosis, and Dreschfeld noted angina pectoris and sudden death in a boy of twelve years.

Graham Steell, in 1906, wrote that "In rheumatic young adults with aortic incompetence angina pectoris is occasionally observed to occur." He also described two of Dr. M. Stanley Wood's cases who showed rheumatic mitral stenosis with angina pectoris; both were women, one twenty-two and the other twenty-four years old. In the first of these two cases the anginal pain began five months before death. At postmortem examination the coronary arteries were reported to be sound. Steell also refers to two other cases of angina pectoris, one a young doctor who died at the age of twenty-seven years, originally reported by Gairdner, and the other a child who dropped dead and showed at postmortem examination syphilitic aortitis and coronary disease.

Walshe, in 1861, and Austin Flint, in 1866, wrote that angina pectoris was very rare under the age of forty years. Incidentally in spite of a fairly large cardiovascular practice Flint saw but few cases of angina pectoris at any age; of 338 patients with organic heart disease whom he analyzed only 15 had angina pectoris, and he wrote on one occasion as follows: "It has so happened that I have not met with a single case of angina pectoris among the large number of cases of cardiac disease which have come under my observation during the last five years." Certainly now, over half a century later

(1927), angina pectoris is much more common. Ninety-nine private patients were seen by us in 1926.

We have found no report of youthful cases in such other works as those of Laennec, Williams (C. J. B.), Watson, Stokes, Swett, Strümpell, Fraentzel, Krehl, Niemeyer, Hoffmann, Poynton and Paine, French, Babcock, Cabot, Coombs, Rotch, Morse, Holt, Pfaundler and Schlossmann, and Abt.

Altogether we have found in the literature fairly definite reports of 42 cases of angina pectoris under thirty years of age. To this group we are adding 8 of our own series, thus making a total of 50 cases under thirty years of age.* There is also an incomplete list of 126 cases of angina pectoris in the literature between the ages of thirty and forty to which we add 7 more, making 133 in all.

We are indebted to Dr. Benjamin for recent reference of two of our youngest cases and to Dr. Morrison for a third.

COMPARISON WITH EARLIEST AGES OF VICTIMS OF CORONARY THROMBOSIS OR EMBOLISM

It is worth while in passing to mention cases of coronary thrombosis in young people in comparison with these of angina pectoris. Christian, in his series of 71 cases of coronary thrombosis from the Peter Bent Bringham Hospital, found 5 under the age of forty years, the youngest being thirty-one. Of Wearn's earlier series of 19 cases there was only 1 under forty years of age. Of 15 cases in a series of cardiac infarction reported by Kerr and his associates there were 4 under forty, 2 of these being cases of coronary embolism in subacute bacterial endocarditis, 1 of them below thirty (aged twenty-five years). Of 23 cases of acute coronary occlusion from the Massachusetts General Hospital cited by Wolff and White no patient was under forty years of age. In another recent series of 95 private patients with coronary thrombosis collected by us there were 2 cases under forty years of age: 1 of thirty-nine and 1 of twenty-six years. Clark has recently reported the case of a naval aviator who died suddenly with coronary thrombosis at the age of thirty years. Werley has published the record of a Mexican laborer with syphilis and coronary thrombosis at twenty-four years of age. Jamison and Hanser have described coronary thrombosis in a youth of eighteen years. Schaps has cited the case of an infant three and one-half months old with myocardial infarct and rupture due to staphylococcus septicemia. The man twenty-six years old included above in our own series of

*Very recently, since the completion of this paper, Schwartz has published a report of 5 patients between the ages of sixteen and twenty years with paroxysmal cardiac pain complicating multiple valvular heart d'sease of rheumatic origin. All five cases had aortic insufficiency and four of them mitral stenosis as well. (Schwartz, Sidney P.: AM. HEART JOUR., 1927, ii, 497.

95 patients is a medical student recently seen by us. The report of his case we expect will be published from Montreal.

Thus it is evident that coronary thrombosis and embolism in young people are even rarer than is angina pectoris. Under the age of thirty the ratio from these figures is 5 to 50 (one to ten), and between the ages of thirty and forty years, 11 to 133. These ratios, like some of the figures, are necessarily inexact.

CASE REPORTS OF PATIENTS WITH ANGINA PECTORIS UNDER THIRTY OF AGE

CASE 1.—Mrs. A. C. B., a physician's wife was examined in 1926 at the age of twenty-five years.

Diagnosis.—Rheumatic heart disease, aortic regurgitation, mitral regurgitation, angina pectoris (of nine years duration, beginning at the age of sixteen years). Pregnancy.

History.—Tonsillitis at the age of three years and repeatedly thereafter until removal of tonsils two years before this examination. Chorea at the age of five years. Heart trouble was discovered soon after this and has been present ever since. There have been murmurs of aortic and mitral valvular disease for the past eight years at least.

Nine years ago at the age of sixteen she first began to have attacks of severe upper substernal oppression radiating down the left arm to the hand (and to the left side of the neck if allowed to continue), lasting about ten minutes; these were brought on more by excitement or cold air than by exertion. These attacks have recurred almost daily since,—an average of three or four spells a day. Seven years ago the patient began to use nitroglycerin by mouth for the pain, always with immediate relief. She uses an average of three tablets daily (1/100 grain each). Except for the pain and very slight dyspnea she has been well. When seen she was three months pregnant and was better than for a long time.

Family History.—Her father has angina pectoris and a sister has rheumatic mitral disease.

Physical examination showed a well-developed and nourished healthy appearing young woman with normal respiration and good color. Her tonsils were absent. No exophthalmos. Pupils were equal and reacted normally to light. No arcus senilis. Thyroid gland was normal. Teeth were in good condition. Cervical glands were not enlarged and cervical veins were not prominent.

The heart was enlarged, the apex impulse and left border of dullness being found in the sixth interspace 9 cm. to the left of the midsternum and 1.5 cm. beyond the midclavicular line. The rhythm was normal and sounds were fair except for absence of the aortic and pulmonic second sounds. A loud, blowing diastolic murmur was heard over the entire precordia but loudest along the left sternal border. There were also basal and apical systolic murmurs of moderate intensity, but no mitral diastolic murmur at the apex and no thrills. The pulse was full in volume and somewhat collapsing in type. The radial arteries were soft. In the neck there was a marked arterial pulse. There were no signs of congestive failure, or edema of extremities or lungs. No clubbing of the fingers was found. Pulse rate was 96 at apex and wrist. Blood pressure was 150 mm. systolic, 50 mm. diastolic. Urine was normal.

Electrocardiogram showed normal rhythm at a rate of 100 with diphasic T-wave in Lead II and inverted T-wave in Lead III.

CASE 2.—C. D. (M. G. H.), a single female Italian dressmaker, was examined in January, 1926 at the age of twenty-two years.

Diagnosis.—Rheumatic heart disease, aortic regurgitation and questionable stenosis, mitral regurgitation and stenosis, angina pectoris (of five years duration beginning at the age of seventeen years). Left cervical sympathectomy.

History.—Rheumatic fever occurred at the age of six years and again on five or six subsequent occasions in the winter time, the last two times in 1924 and in January, 1925. Five years ago she began to have attacks of oppressive pain in the left anterior chest, under the sternum and down the left arm, coming at any time but more often on exertion. As this symptom increased in frequency and severity, coming even when quiet in bed, she was admitted to the hospital ward early in 1923 where she was studied for weeks. At first a neurosis was suspected, and then paroxysmal tachycardia, but repeated observation of the attacks convinced us of the reality of the angina pectoris. She was frequently awakened at night by the pain. She would become excited and at times cried out with the severity of the attacks. The pulse rate and blood pressure were both increased during the attacks. The pain would last for from ten to twenty minutes and then would gradually die down. Finally nitroglycerin was administered, with rapid relief of all of the attacks of pain while in the ward and since. She used this drug daily, and in the winter of 1925-1926 the angina pectoris became so bad that cervical sympathectomy was advised and carried out in February, 1926. In the October before operation she used as many as 200 tablets (1/100 grain each) of nitroglycerin in ten days. There have been no other important symptoms.

Physical Examination showed a well developed and well-nourished young woman with mitral facies and increased venous pulsations in the neck. The heart was markedly enlarged, the maximal apex impulse and left border of dullness being found in the sixth intercostal space 11 cm. to the left of the midsternum and 3 cm. beyond the midclavicular line. There were rough blowing systolic and loud blowing diastolic murmurs at the base, the former heard best in the aortic area and the latter along the left sternal border. The pulse had a waterhammer quality, but the rhythm was normal except for rare premature beats. The heart rate was 90. The blood pressure was 175 mm. systolic and 30 mm. diastolic.

Electrocardiogram showed normal rhythm in May, 1923, with well-marked abnormal left axis deviation. In January, 1924 during an attack of angina pectoris an electrocardiogram showed sinoauricular tachycardia at a rate of 140. And in January, 1926 the electrocardiograph showed normal rhythm with a rate of 100 and abnormal left axis deviation as before.

X-ray films in May, 1923 showed an enlarged heart with the following measurements by teleroentgenogram: MR, 6.0 cm.; ML, 11.5 cm.; T, 17.5 cm.; Gt. Ves., 8.0 cm.; Int. Diam. Thorax, 24.5 cm. Cardiothoracic ratio $\frac{17.5}{24.5} > \frac{1}{2}$.

Wassermann reaction negative; blood, urine, and renal function (red) tests were normal.

Left cervical sympathectomy was performed by Dr. E. P. Richardson in February, 1926. The superior cervical ganglion was excised. For the following month there was little or no pain, and then after an acute respiratory infection it began to reappear. In April, 1926, two and one-half months after the operation, the angina pectoris was about one-half as frequent and severe as before the operation, but considerable nitroglycerin (several tablets daily) was being used, always with quick relief.

Later note.—Jan. 12, 1927. The patient has been in bed for three weeks until today. She looks exhausted and pain is felt in her left arm constantly. She has four or five attacks of pain daily lasting five or six minutes. Up to three weeks ago she was taking nitroglycerin (5 or 6 pills daily) and digitalis (1 pill daily).

Three weeks ago she called a local physician who prescribed a liquid medicine. The patient thinks that it has helped her. She thinks the operation has not benefited her. She will come to the clinic as soon as she feels well enough. (Kindness of Miss N. Upton.)

CASE 3.—M. M. (M. G. H.), a single male Greek cotton mill worker, was examined in April, 1913, at the age of seventeen years.

Diagnosis.—Rheumatic heart disease, aortic regurgitation and questionable stenosis, mitral regurgitation and stenosis, questionable adherent pericardium, angina pectoris (of four months duration, beginning at age of seventeen years).

History.—Rheumatic fever occurred at the age of eleven years and again at thirteen years. Four months before examination the patient began to feel attacks of heavy pain in the front of the left chest; these occurred frequently at night and were quickly relieved by nitroglycerin. There was also some dyspnea.

Physical examination showed a well-developed and nourished young man, with ragged tonsils. The heart was much enlarged, the apex impulse and left border of dullness being found in the sixth intercostal space 5 cm. beyond the nipple line. The rhythm was regular, and the heart rate was 65 to 80. There was a systolic thrill in the interclavicular notch. Both heart sounds at apex and base were masked by loud systolic and diastolic murmurs. The pulse showed a waterhammer character.

X-ray films showed a very large heart with the greatest transverse diameter 16 cm., great vessels 6.5 cm. wide, and the apex impulse in the sixth space 13.5 cm. to the left of the midsternum. Electrocardiogram was not obtained (galvanometer not yet installed). Wassermann reaction negative. Urine and blood normal.

CASE 4.—G. G. (M. G. H.), a male Italian worker in screw factory, was examined September, 1926 at the age of nineteen years.

Diagnosis.—Rheumatic heart disease, aortic regurgitation and stenosis, mitral regurgitation and stenosis and angina pectoris (of six months duration, beginning at the age of eighteen years).

History.—Tonsillitis occurred several times in the past with tonsillectomy two years before this examination. Rheumatism began in various joints three years ago, with recurrence of acute rheumatic fever fifteen months ago for which he was admitted to the hospital ward (June, 1925). At that time he showed aortic regurgitation and mitral stenosis. In April, 1926, six months before the present examination, he began to have precordial pain and substernal oppression on exertion for which in the out-patient department he was given nitroglycerin, with rapid relief on every occasion. This symptom increased until now it may even awaken him at night, generally after or during a dream. He has not stopped work and he goes to bed late.

Physical examination showed a well-developed and nourished young man. Reflexes normal (pupils and knee-jerks). Tonsils removed. Forceful arterial pulse in neck. The heart was moderately enlarged, the apex impulse and left border of dullness being found 10 cm. to the left of the midsternum and 2 cm. beyond the midclavicular line. There was no abnormal supracardiac dullness. A systolic thrill was palpable in the second right interspace near the sternum. A loud blowing diastolic murmur was heard best along the sternum, especially in the second right interspace. There was a slight middiastolic rumble at the apex. The pulse rate was 80 and blood pressure 120 mm. systolic and 35 mm. diastolic. The lungs were clear, and there was no edema over the shins.

Electrocardiogram showed normal rhythm with a rate of 100 and rather large P-waves in Lead II. The x-ray films showed only slight enlargement in 1925. The blood, urine and Wassermann reactions were all negative.

CASE 5.—R. M., a single traveling salesman, was examined Dec. 29, 1926 at the age of twenty-four years.

Diagnosis.—Rheumatic heart disease, aortic regurgitation, and angina pectoris (of 5 months duration, beginning at the age of twenty-four years), subacute bacterial endocarditis.

History.—Rheumatic fever which occurred twelve years before present examination affected the heart. Diphtheria a few months later, pneumonia eight years ago, and a nervous breakdown five years ago have been the only other illnesses in the past.

Five months previous to this examination substernal oppression on exertion in the cold air was first experienced. This was transient, lasting a few minutes,—never more than fifteen. The pain radiated only a short distance outward from both sides of the sternum, never to the epigastrium, neck, or arms. It has continued to occur almost daily on exertion ever since its onset, sometimes as often as three or four times a day. It never comes when quiet, except rarely on waking up after an exciting dream. It comes more often on exertion after meals than before meals. Two months ago the patient began to use nitroglycerin which stops the pain almost instantly. He uses about three 1/100 grain tablets every week. Except for the attacks of pain and slight dyspnea on exertion he feels well and works daily. He drives a car in his work. *Family history* is negative.

Physical examination showed a well-developed and nourished healthy appearing young man with normal breathing and good color. Reflexes (pupils and knee-jerks) normal. No arcus senilis. Thyroid gland normal. No exophthalmos. Tonsils enlarged. Teeth rather neglected. Cervical veins not engorged. Heart moderately enlarged, the apex impulse and left border of dullness being found in the fifth intercostal space 10 cm. to the left of the midsternum and 1.5 cm. beyond the midclavicular line. There was no abnormal supracardiac dullness. The rhythm was normal and the heart sounds were of fair quality. Along the left sternal border there was heard a loud, blowing, diastolic murmur, not well heard at the apex. There were systolic murmurs at the aortic area and at the apex, moderately loud in the former location and but slight in the latter. There was no mitral diastolic murmur. There were no thrills and no precordial tenderness. The pulse was of waterhammer character. The artery walls were soft. The lungs were clear and there was no edema over the shins. The fingers were clubbed but not cyanotic. The pulse rate was 96 at the apex and wrist, the blood pressure 145 mm. systolic and 25 mm. diastolic. The temperature was 98.2° F.

Tonsillectomy was advised, and, because of the clubbing of the fingers, study was recommended to see whether or not an insidious subacute bacterial endocarditis might be in progress. Later note: Cerebral embolism and other findings after a few months proved the presence of subacute bacterial endocarditis.

CASE 6.—D. W. (M. G. H.), single male Irish rubber coat maker, was examined November, 1901 at the age of twenty-six years.

Diagnosis.—Rheumatic heart disease, aortic regurgitation, mitral regurgitation, and angina pectoris (of a few weeks duration, beginning at the age of twenty-six years). Acute bronchitis. Death. No autopsy.

History.—Rheumatic fever occurred ten months before examination and again six weeks before. While sick at home a few weeks ago he began to have left anterior thoracic pain, radiating down the left arm, lasting only a minute or two, with uncertain relation to exertion. This pain increased in frequency and severity so that finally he was admitted to the hospital ward, suffering ten or twelve attacks of pain a day. He had been growing short of breath also and had lately caught cold.

Physical examination showed a well-developed and nourished young man ill in bed with some fever (100°-102° F.), tachycardia (pulse rate 100-120) and increased respiratory rate (25-40). There was a marked arterial pulse in the neck.

The heart was considerably enlarged, the apex impulse being recorded as 10 cm. and the left border of dullness 12 cm. to the left of the midsternum. A loud blowing diastolic murmur was heard all over the precordia but loudest in the fourth intercostal space just to the left of the sternum. There was a blowing systolic murmur loudest at the apex. The pulse was waterhammer in character and a capillary pulsation was visible. His lungs showed apparently acute bronchitis. The urine was normal and the white blood cell count was 11,000.

After two weeks in the ward he had prolonged left arm and chest pain, which was only slightly relieved by nitroglycerin and morphine. He died. There was no postmortem examination.

We can only surmise as to the cause of death. It seems likely that it was coronary occlusion due to thrombosis or embolism. The previous attacks of angina pectoris would favor this diagnosis.

CASE 7.—A. O. (M. G. H.), single male Jewish schoolboy, aged twenty years in April, 1927, was examined first in October, 1915 and about once a year subsequently.

Diagnosis.—Rheumatic heart disease, aortic regurgitation and stenosis, mitral regurgitation and stenosis, adherent pericardium, questionable paroxysmal tachycardia or fibrillation, angina pectoris (probably of eight years duration, beginning at the age of twelve).

History.—(April, 1927) Rheumatic fever occurred at the age of five years, and was followed by several other attacks during the next three years. Sore throat was noted frequently during this time. Moderate palpitation and dyspnea were experienced following effort. Eight years ago, after an attack of influenza, the patient complained of nocturnal attacks of severe precordial and midsternal distress followed by moderately rapid heart action. These attacks lasted from twenty minutes to one hour, and were frequently terminated by forced vomiting.

Six years ago the patient experienced a severe respiratory infection and remained in bed two months thereafter. From 1923 to 1925 he felt fairly well and attended school. His activity was limited to a moderate degree, but he was able to "carry on" without medicine.

Two years ago he had a nervous breakdown from overwork and experienced marked increase in frequency and duration of the nocturnal "attacks" which consisted of oppression in the chest, numbness in the arms, dyspnea, and salivation. These attacks occurred almost every night, and interfered with the patient's rest. Quinidine sulphate, grains 3, morning and night, and digitalization followed by daily rations of 1½ grains of digitalis improved the patient's condition slightly.

In March, 1925, two or three attacks were experienced each night. These were similar to those noted above except that they were associated with sharp pain in the right chest and in both axillae and were accompanied by a low substernal choking sensation. The attacks were sudden in onset, often awaking the patient from sleep. A few months later he had another nervous breakdown. Digitalis and quinidine sulphate did not affect these nocturnal attacks.

One year ago he remained in bed for two months because of backache, weakness, and nervous instability. At this time the attacks of pain at night radiated to the right arm, and were definitely and promptly relieved by nitroglycerin. In January, 1927, the attacks were noted, particularly after excitement, but also occurred during the night. Nitroglycerin gave instant relief and the patient averaged five or six 1/100 grain tablets a day. Aside from this symptom his chief complaints were nervousness and palpitation.

In May, 1927, he died suddenly.

Physical Examination (April, 1927).—Fairly well-developed, but thin. Cheeks flushed. Skin pale. The heart was very large; the apex impulse and left border of dullness were in the seventh intercostal space in the midaxillary line 13 cm. to

the left of the midsternum, and 4.5 cm. to the left of the midclavicular line. The right border of dullness in the fourth interspace was 4.5 cm. from the midsternum. Over the aortic area there were loud systolic and harsh diastolic murmurs associated with short diastolic and marked systolic thrills. There were loud systolic and low-pitched mid-diastolic murmurs at the apex. A well-marked Broadbent's sign was present. The pulse was regular and semi-Corrigan in type. The apex and radial rate was 80 per minute. Blood pressure was 150 mm. systolic, 10 mm. diastolic. An auscultatory gap was noted between 120 mm. and 90 mm. The lungs were clear, liver was not enlarged, and there was no edema of the shins. A typical anginal attack was observed at the beginning of this examination, but did not become severe because the patient took nitroglycerin at once. This attack consisted of substernal fullness, pain in the right axilla, sweating, and bounding pulse with some increase in rate.

An electrocardiogram (June, 1921) showed normal rhythm; rate of 90; very high R-wave in Lead II; inverted T in all leads; inverted P in Lead III, upright Q in Lead II. X-ray films of the heart, in February, 1927, showed a cardiac shadow markedly enlarged in all directions. Considerable hypertrophy of the left ventricle, and some tortuosity of the aorta were noted. The following measurements were made by teleroentgenogram: R = 6.1 cm., L = 13.4 cm., T = 19.5 cm., GV = 7.5 cm., internal diameter of the thorax = 26.5 cm., cardiothoracic ratio $= \frac{19.5}{26.5} > \frac{1}{2}$.

CASE 8.—A. L. M., Jewish male law student, aged twenty-three years when examined as private patient Feb. 26, 1927.

Diagnosis.—Rheumatic heart disease, aortic regurgitation, and angina pectoris (of five years duration, beginning at the age of eighteen years).

Present Illness.—Five years ago, at the age of eighteen, while in bed recovering from a severe attack of rheumatic fever, he suddenly suffered marked high substernal oppression radiating outward and upward to the left shoulder and down the left arm to the elbow, lasting a few minutes. Attacks of pain similar to this first one recurred several times a day, lasted sometimes as long as half an hour and were relieved by vomiting. At first indigestion was diagnosed, but after ten days angina pectoris was suspected and nitroglycerin was given, with complete and rapid relief.

The attacks of pain have recurred ever since their onset five years ago, usually every day, but varying from four or five times in one day to once in four or five days. They are brought on by exertion, excitement, cold air, and especially after meals. Four or five nitroglycerin tablets are required daily on the average, but from none to twelve a day may be needed. He has been much limited in his activity and studies by the liability to pain. During the past year or two the attacks have grown less severe and less frequent, not radiating to the arm at present. He now and then wakes up at night with substernal oppression following an exciting dream.

He has had no other symptoms and feels very well except for the pain. He wants to marry.

Past history.—Rheumatic fever occurred twice, at six and at eighteen years of age. Chorea occurred at eight years of age, and tonsillitis repeatedly, with operations for tonsillar removal at the ages of fifteen and twenty-two years. Diphtheria occurred in early childhood but he had no other illnesses. His heart was affected at the time of his first rheumatic fever and this fact has always occasioned limitation of his athletic activities.

Habits are good. No tobacco or alcohol. Little tea and coffee. Bowels regular.

Family history.—Mother recently has had rheumatic fever and a sister has a "rheumatic" heart.

Physical examination (Feb. 26, 1927) revealed a rather slight but healthy appearing young man with normal breathing and fair color. He was mentally alert. His pupillary reactions were normal. His tonsils were absent. There was no exophthalmos and his thyroid gland was normal. His teeth showed much dental work. The cervical glands were not enlarged and the cervical veins were not engorged, but there was a large arterial pulse in the neck.

His heart showed well-marked enlargement, the apex impulse being felt in the sixth intercostal space 10.5 cm. to the left of the midsternal line and 2.5 cm. beyond the midclavicular line. The left border of percussion dullness corresponded to the apex impulse. There was no abnormal supracardiac dullness. The sounds were of good quality. There were moderately loud blowing systolic and diastolic murmurs over the precordia, loudest in the second right intercostal space near the sternum but also heard, though much less distinctly, at the apex. In the recumbent position there was also heard at the apex a slight middiastolic rumbling murmur (quite possibly an Austin Flint murmur). The heart rhythm was normal. There were no thrills or tender spots over the precordia. The pulse was Corrigan in character and the artery walls were soft. The pulse rate was 78 at both apex and wrist. The blood pressure was 160 mm. systolic and 25 mm. diastolic. The electrocardiogram showed normal rhythm, with a rate of 110, left axis deviation, deeply inverted T-waves in Leads I and II, and abnormal QRS complexes in Leads I and III.

The lungs and abdomen were normal. The left anterior chest wall was more prominent than the right. Liver and spleen were not felt. There was no edema of the extremities or clubbing of the fingers. The knee jerks were equal and very active.

DISCUSSION

The mechanism of angina pectoris is as little known in our cases, or in any of the young people reported in the literature, as it is in the common instances in older patients. One observation, however, is probably important with respect to the etiology. In every one of our eight cases rheumatic aortic regurgitation was present. Evidence of aortic stenosis, mitral stenosis, congestive failure, or acute infection was much less constant. This relationship between rheumatic aortic insufficiency and angina pectoris in youth has been noted before, among others by Steell and by Levine. Of course the relationship between angina pectoris and luetic aortitis with or without aortic regurgitation is too well known to demand more than passing mention. Whether in these rheumatic hearts the aortic regurgitation itself, by the decrease in coronary circulation associated with a low diastolic pressure, or whether involvement (in the rheumatic infection) of the coronary arteries (arteritis) or of the aorta (rheumatic aortitis) associated with the contiguous aortic valve disease, may be responsible for the angina pectoris we do not know. Perhaps two of these conditions or even all three, or, on the other hand, some other unknown factor, may be to blame. The association is certainly interesting. Another fact may be of some importance. Exertion was of less significance in bringing on an attack of pain than is usually the case in angina pectoris. The attacks were very apt to come on with the pa-

tient quiet and even in bed, although excitement did favor their occurrence.

Among the cases in the literature aortic regurgitation is not the only finding recorded on physical examination. Mitral stenosis has been found in a number of cases, apparently without aortic valve disease. This is, however, a rheumatic manifestation and it may prove to be the rheumatic infection itself, perhaps involving artery walls, that is the important factor rather than the type of valvular disease. Finally in one fatal case of Osler's in a young man of twenty-six years no gross lesions whatever were found, either on physical examination or at autopsy. Another case of Osler's, however, a man of twenty-four years, showed at postmortem examination aortitis, apparently luetic, with coronary arterial disease. Four other patients in Osler's series, aged thirty-four, thirty-seven, thirty-eight and thirty-nine years respectively, were syphilitic. They were autopsied. Two of them showed "normal coronary arteries."

Note may be made here of an instance of angina pectoris at the Massachusetts General Hospital a few years ago in a man of thirty-one years with subacute bacterial endocarditis and a large vegetation on one of the aortic cusps blocking the mouth of the left coronary artery; at postmortem examination the aorta and coronary arteries were found normal otherwise. This case was reported in the Cabot Case Records. The fact that coronary sclerosis and thrombosis can occur in individuals under thirty years of age suggests of course that arterial changes alone, not dependent on rheumatic or luetic infection, may be responsible for angina pectoris in rare cases.

This group of young patients may eventually aid us a great deal in the solution of the difficult problem of the mechanism of angina pectoris. Postmortem examinations carefully carried out in this presclerotic age group of angina pectoris should reveal something of interest.

In closing the discussion it should be said that the prognosis in these young people with angina pectoris appears to be fairly good, the duration of life after the onset of the symptom of pain being considerably greater than the average of large groups of all ages.

SUMMARY

A report is made of eight cases of angina pectoris in young people below the age of thirty years. In a review of the literature 42 other cases are noted. Angina pectoris though very rare in persons under thirty years old is much more common (by about 10 to 1) than coronary occlusion (by thrombosis or embolism) at the same age.

All of the eight cases reported here had one uniform finding—rheumatic aortic regurgitation.

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MYXEDEMA HEART*

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IF DILATATION of the heart, dyspnea on exertion, anasarca of the dependent portions of the body, passive congestion of the liver, and edema of the lungs are symptoms of heart failure, then heart failure of greater or less degree is not very infrequent in myxedema. If the complete or nearly complete relief of these symptoms by medication with thyroid extract in amount sufficient to bring the basal metabolism up to the normal and to cause the myxedema to disappear is evidence that both the myxedema and the heart failure have the same cause, namely, thyroid deficiency, then the term myxedema heart is justified.†

We reported, in 1925, two cases of heart failure undoubtedly caused by the thyroid deficiency, which is the basis of myxedema.[1] These two cases were apparently cured by thyroid medication. Previous to our publication Zondek[2, 3] had reported six cases of heart failure due to thyroid deficiency which were cured by thyroid medication. One of Zondek's cases was very much like an experimental proof of the reality of myxedema heart. A German officer received a bullet wound in the neck in 1914; the wound was infected and pus drained from the neck in 1914 and 1915. Slowly the symptoms and signs of myxedema developed and three years after the wound infection there was a fully developed case of myxedema with heart failure symptoms. The heart was very much dilated on x-ray examination. The electrocardiogram showed no P-wave or T-wave in Lead I. The symptoms of myxedema and heart failure disappeared on thyroid extract therapy and the teleroentgenogram of the heart revealed a normal size and shape and the electrocardiogram now revealed P- and T-waves in Lead I. Zondek believes there was an acute purulent thyroiditis with destruction of the parenchyma of the thyroid and consequent hypothyroidism in this case. In addition to these six cases of Zondek in the German literature, Assman[4] has described one case of myxedema with heart failure symptoms and dilated heart in which digitalis had no effect upon the heart failure but in which thyroid extract relieved both the myxedema and the heart failure symptoms and caused a re-

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†The name myxedema heart was applied by Zondek to this condition in his first paper in *Muenchener Medizinische Wochenschrift*, 1918, lxv, 1180. As he was the first physician to point out the outstanding features of cardiac failure in myxedema, the name applied by him should stand despite the fact that the name might be improved upon.

duction of 4 cm. in the transverse diameter of the heart, as determined by the teleroentgenogram. Also in the German literature Meissner[5] has described one case of myxedema of twelve years' standing with heart failure symptoms and on x-ray a transverse diameter of the heart of 20.5 centimeters. On thyroid extract treatment the myxedema and heart failure symptoms disappeared and the dilatation of the heart regressed 5 centimeters. Curschmann[6] also describes a case of heart failure with marked cardiac dilatation. The heart failure in this case also disappeared and the cardiac dilatation was reduced by thyroid medication.

In the French literature there is a report of one case of myxedema heart by Laubry, Mussio-Fournier, and Walser[7] in which the dyspnea, anginal attacks and cardiac dilatation as determined by the orthodiagram disappeared on thyroid medication.

In this country Means, White, and Krantz[8] have described one case of uncomplicated myxedema heart with the characteristic dilatation and T-wave negativity with return to normal on thyroid medication.

On the other hand Willius and Haines[9] in a paper on *The Status of the Heart in Myxedema* have the following conclusions: "In 162 cases of high grade myxedema studied, none of heart failure and none of organic cardiovascular disease was found that could be justly attributed to the myxedema. There were numerous electrocardiographic abnormalities which disappeared under thyroid medication. The data presented do not justify the establishment of a cardiac syndrome characteristic of myxedema."

Willius and Haines' conclusions are very hard to understand. With the largest material of myxedema cases in the world they have been unable to find a single case of cardiac failure attributable to myxedema, whereas in other clinics where the amount of material is very much smaller numerous cases of heart failure unquestionably due to the same factors as the myxedema have been found. In the past four years we have seen just six cases of myxedema at the General Hospital and the University Hospital. All six cases showed more or less heart failure, the symptoms and signs of which receded partially or completely on thyroid medication.

One other case of myxedema was in the University Hospital during this period but as it had been on thyroid medication before our attention was called to it, we made no effort to study this case. The teleroentgenogram in this case, which will not be included in our series, was taken after the patient had been on thyroid extract for some days and showed no apparent enlargement of the cardiac shadow. It is very possible that this patient had no signs of heart failure before thyroid medication was started. On the other hand, the six cases studied by us and reported upon in this paper, all showed some subjective symptoms and some objective signs of heart failure.

Case 1 has already been described in our first paper on *Myxedema Heart*,[10] but as it is the most striking of our cases and has now been followed for four years, we shall report it in this paper.

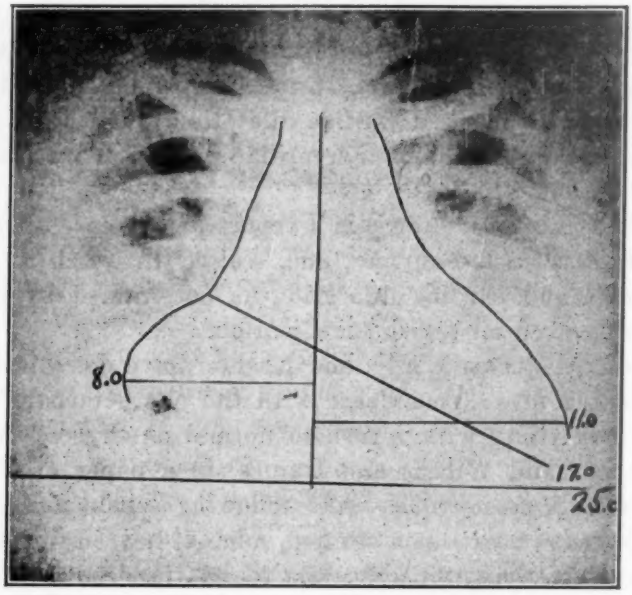

Fig. 1-*A*.*—Teleroentgenogram of Case 1 before any thyroid extract was given. Ml=11.0; Mr=8.0; T=19.0. All illustrations have been retouched. Three roentgenographers drew in the outlines of the hearts and measured the diameters. The author made none of the measurements.

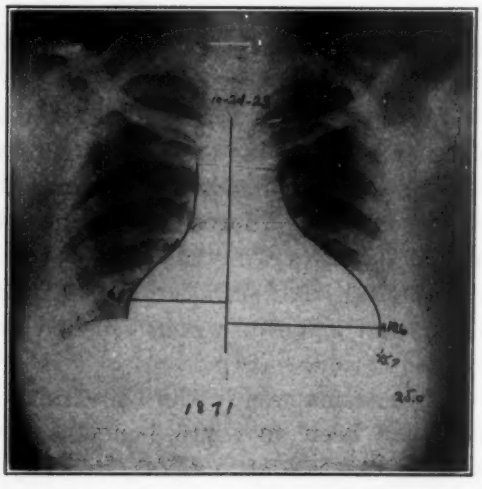

Fig. 1-*B*.—Teleroentgenogram of Case 1 taken after patient had been only twelve days on thyroid extract, eight grains a day. Ml=10.6; Mr=6.8; T=17.4.

Case 1.—Female, aged forty-six years, entered the General Hospital with present complaint of shortness of breath, swelling of the legs, palpitation of the heart, and great weakness. The patient stated that she had had some dropsy and dyspnea on exertion, off and on for eleven years previous to this admission, and had been pretty largely incapacitated for the six years previous to this hospital admission.

*Figs. 1-4 were first published in the *Jour. Am. Med. Assn.*, 1925, lxxxiv, 345.

There was a history of loss of memory, slow and difficult cerebration, dry skin, puffy eyes, loss of hair, and cold extremities for eleven years. Two years previous to this admission she was in the General Hospital with symptoms of heart failure at which time the diagnosis on the case record was "myocarditis, chronic valvular disease,

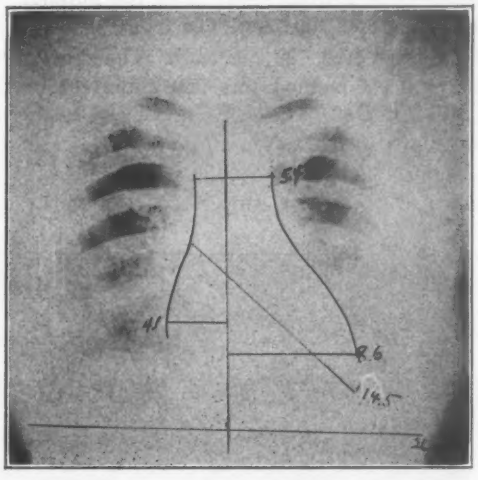

Fig. 2.—Teleroentgenogram of Case 1 taken seven weeks after Fig. 1A and after patient had had eight grains of thyroid extract each day. Mi=8.6; Mr=4.1; T=12.7. The diaphragm is not quite one-half interspace lower in Fig. 2 than in Fig. 1-*B*.

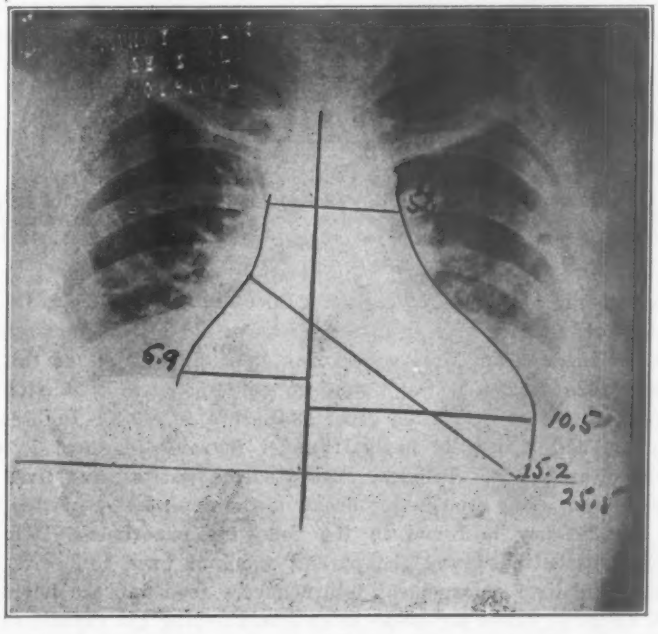

Fig. 3.—Teleroentgenogram of Case 1 taken six weeks after complete withdrawal of thyroid extract. Mi=10.5; Mr=5.9; T=16.4. Diaphragm on right side one-half interspace higher than in Fig. 2.

mitral insufficiency, myxedema." The patient was orthopneic, there was edema of the lower extremities, there was ascites, the liver was four centimeters below the costal margin in the right medioclavicular line, there were fine and medium-sized râles at both bases and the heart was enormously dilated in all chambers (see Fig.

1). The skin of the face was sallow with characteristic cyanotic patches over the malar prominences. The eyes were puffy, the palpebral fissures were small, and the face was swollen and expressionless. The skin was dry and scaly, the hair very sparse. The fingers were enlarged from myxedematous infiltration. The speech was slow and the voice hoarse. The blood pressure was 110/70, the pulse rate around 70. The temperature tended to be a little lower than the normal. The hemoglobin was 75 per cent and the red count 3,700,000. The urine showed a trace of albumin at times. The basal metabolism was −25 per cent. The diastolic volume of the heart as determined by Bardeen's[11] method was 950 cubic centimeters or just twice as large as the mean normal heart of a female of this size.

The symptoms and signs of cardiac failure in this patient were very little improved by rest in bed and digitalis therapy continued for three weeks. The teleroentgenogram taken at the end of this period of rest in bed and digitalis ther-

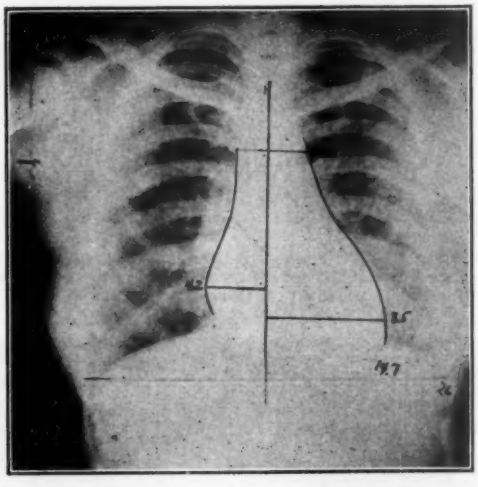

Fig. 4.—Teleroentgenogram of Case 1 taken six weeks after Fig. 3.
During the previous five weeks the patient had eight grains of thyroid extract per day. Diaphragm about one interspace lower in Fig. 4 than in Fig. 3. Diaphragm position cannot explain difference in heart size. Ml=8.5; Mr=4.2; T=12.7.

apy is shown in Fig. 1. Thyroid extract (Burroughs Wellcome & Co.) 0.48 gram per day, was now prescribed and in seven weeks the teleroentgenogram shown in Fig. 2 was obtained. The basal metabolism was +5 per cent at this time. This heart shadow when measured was found to correspond to a diastolic volume of 490 cubic centimeters as calculated from Bardeen's formula. In other words, the previous volume had shrunk to one-half under thyroid treatment in seven weeks' time. In the meantime the dyspnea, pitting edema, ascites, and liver enlargement had all disappeared. But even better proof of the dependency of this heart failure on thyroid insufficiency is found in the following experiment. Thyroid extract treatment was discontinued and the patient was put back to bed. The dyspnea, pitting edema, and liver enlargement returned very soon and the teleroentgenogram of the heart (Fig. 3) taken six weeks after discontinuing the thyroid extract showed a dilatation of 3.7 cm. in transverse diameter. The basal metabolism at this time was −20 per cent. Again thyroid extract was given and in five weeks the basal metabolism was +5 per cent. The heart was again reduced to normal size (Fig. 4) and the symptoms of heart failure had disappeared.

The case seemed at this time to be an uncomplicated case of myxedema heart. That this was probably not altogether true will be

shown when we discuss the further observation of this case now extending over four years from the time of discharge from the General Hospital. This patient's electrocardiogram will then be discussed also.

CASE 2.—The patient entered the General Hospital on the surgical service only about four months after Patient 1. She complained of weakness, loss of memory, dyspnea on exertion, and pain in the abdomen. She was diagnosed myxedema by

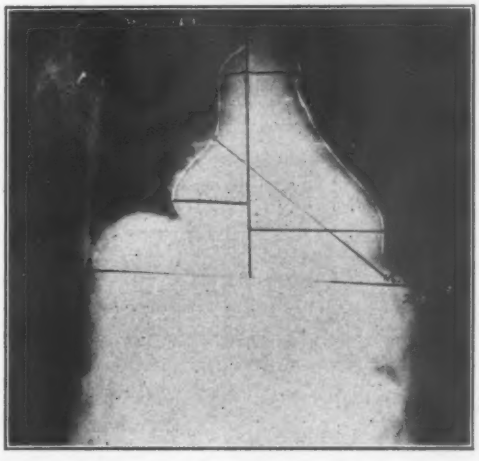

Fig. 5.—Teleroentgenogram of Case 2 before being put on thyroid extract. Ml=10.3; Mr=5.7; T=16.0.

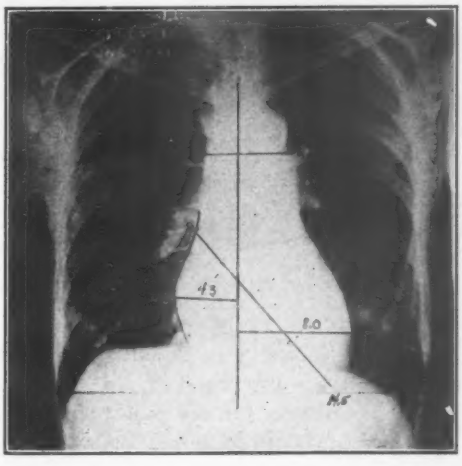

Fig. 6.—Teleroentgenogram of Case 2 after five weeks of thyroid extract treatment, eight grains per day. Ml=8.0; Mr=4.3; T=12.3.

the medical consultant, without much difficulty. The basal rate was −21 per cent and the teleroentgenogram (Fig. 5) shows a heart dilated in all chambers. The hemoglobin was 75 per cent and red count 3,800,000. The electrocardiogram showed T negative in Lead I and isoelectric in Lead II. After taking 0.18 gram Burroughs and Wellcome thyroid extract three times a day for five weeks the basal metabolism went up to −3 per cent, the dilatation of the heart was reduced by about 4 cm. in transverse diameter (Fig. 6), the electrocardiogram showed a positive T in Leads I and II and the symptoms of myxedema had disappeared.

CASE 3.—A woman, fifty-five years old, came to the University Dispensary in August, 1924, complaining of pitting edema of the ankles of two years' duration, dyspnea on exertion of two years' duration, hoarseness of the voice of some years' duration, and attacks of dizziness. There is no record of any physical examination at this time. The patient was treated a few times at the Dispensary but became dissatisfied and left to seek aid from private physicians. She drifted about from one physician to another until one physician felt that an x-ray film of her heart might be an aid in diagnosis. He sent her to Dr. Rigler in February, 1926. Dr. Rigler had made the x-ray examinations of our first two patients. On the basis of the x-ray examination of the heart, Dr. Rigler made a tentative diagnosis of myxedema heart. Through arrangement with her physician, she was sent to the University Hospital to be studied by us. Fig. 9 shows the teleroentgenogram of her heart just before entrance to the hospital at which time her basal metabolism was −35 per cent. Her complaints were shortness of breath of four years' duration, swelling of the ankles which would come on late in the afternoon for the past four

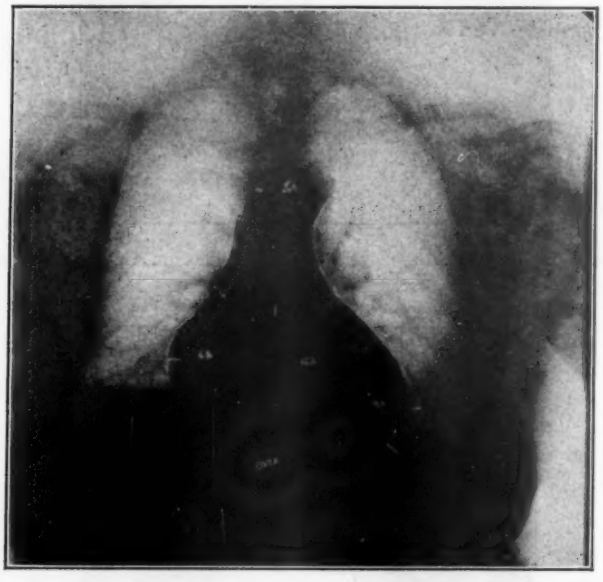

Fig. 7.—Teleroentgenogram of Case 3 before taking thyroid extract. Ml=9.0; Mr=6.2; T=15.2.

years, dry skin, loss of memory, difficulty in thinking, slow speech, partial loss of hearing, pain over the heart at times for past two years, this pain necessitating recumbent position, and marked weakness for the past four years.

Physical examinations made by me before the patient entered the hospital revealed a woman whose cerebration was so slow and uncertain that she needed an attendant to bring her to my office. Her memory was very poor and her speech slow. The face was swollen and all lines of expression washed out. The skin of the face was sallow and there was a small patch of cyanosis on each cheek and the lips were cyanotic. The eyelids were swollen and the palpebral fissures small. There was marked dyspnea on walking about and moderate dyspnea when the patient sat in a chair. There were numerous fine moist râles at both bases on inspiration. The heart sounds were fainter than the normal. There were no murmurs. The liver was about two centimeters below the costal margin in the right medioclavicular line. There was no demonstrable enlargement of the spleen and no demonstrable ascites. There was pitting edema of moderate degree from the knees down to the ankles.

The skin was dry. The teleoroentgenogram of the heart (Fig. 7) shows the decided generalized enlargement of the heart silhouette. The patient was put on thyroid extract. She then went home to make arrangements for entering the University Hospital, which she did three weeks later. She was on three grains of thyroid extract a day for about three weeks before entrance to the hospital. On entrance, the dyspnea was already much less pronounced, the liver had receded to the costal margin, and the pitting edema of the lower extremities was also much less pro-

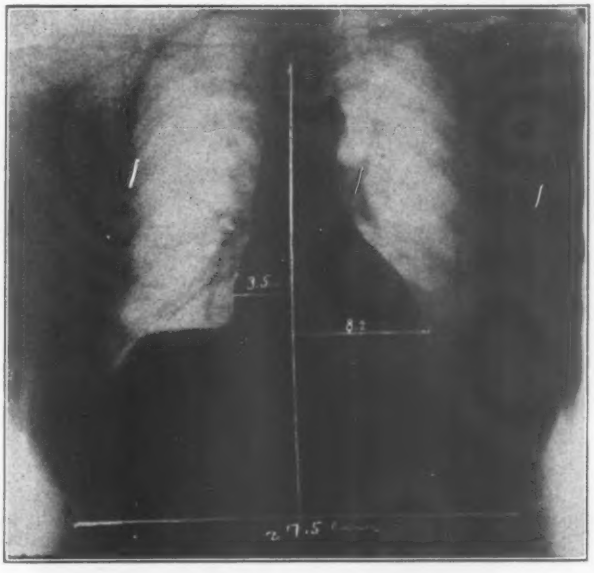

Fig. 8.—Teleroentgenogram of Case 3 after being on thyroid extract for five weeks. Ml=8:2; Mr=3.5; T=11.7. Diaphragm not quite one-half interspace lower than in Fig. 7.

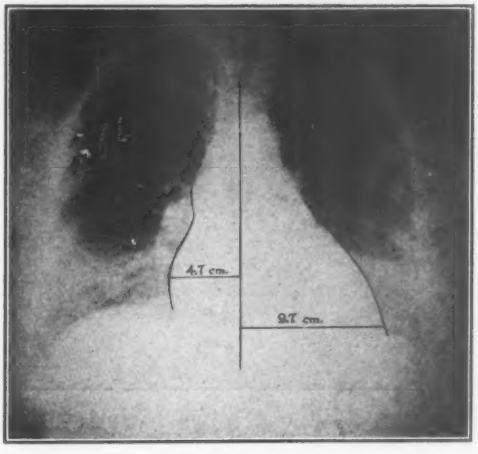

Fig. 9.—Teleroentgenogram of Case 4 before thyroid extract. Ml=9.7; Mr=4.7; T=14.4.

nounced. Her basal metabolic rate was −25 per cent on entrance to the hospital. The hemoglobin was 75 per cent and the red count was 3,800,000 on entrance. The urine contained large quantities of albumin. Dr. Berglund took over the study of the case at this point, he being interested in her as an example of nephrosis. His observations will be published elsewhere. Suffice it to say here, that since leaving

the hospital I have followed her for over a year during which time there have been no signs of albumin in the urine. In the hospital the thyroid medication which started three weeks before entrance was continued for ten days. The heart size was then nearly normal. Râles at the bases had disappeared, the cyanosis had disappeared, and the pitting edema was gone. She was taken off the thyroid extract at Dr. Berglund's request and in nineteen days pitting edema had returned. There was cyanosis over the malar prominences, and at the finger tips. The liver could

Fig. 10.—Teleroentgenogram of Case 4 after five weeks of thyroid extract. Ml=9.0; Mr=4.0; T=13.0. Diaphragm is one-half interspace higher than in Fig. 9.

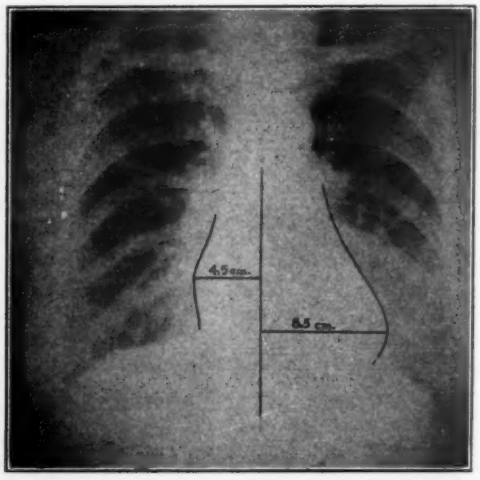

Fig. 11.—Teleroentgenogram of Case 5 before thyroid extract. Ml=8.5; Mr=4.5; T=13.0.

now be felt below the rib margin in the right medioclavicular line on inspiration. The heart sounds were noted by me at this time to be weaker than they were before stopping the thyroid extract. The basal metabolism at this time was −28 per cent. The patient was off the thyroid extract for six weeks and was then put back on six grains a day. Fig. 8 shows the heart shape and size as revealed by a teleoroentgenogram seven weeks after resuming thyroid extract. The heart shape and size were now normal. There were no longer any subjective symptoms or objective signs

of heart failure. In this case also the signs and symptoms of out-spoken heart failure are dependent upon the same condition as the myxedema. When thyroid extract was given the symptoms and signs of heart failure disappeared. When the thyroid extract was withheld, decompensation and dilatation of the heart developed, and when thyroid was again given the heart returned to normal in size, and the symptoms of failure disappeared. The patient has now been performing the usual duties of a housewife with practically no signs of heart failure for seven months. Interesting data obtained in the continued study of this patient will be given below when we discuss complications.

CASE 4.—This patient came to the University Dispensary on account of weakness and a tired feeling during the previous year. In addition she had noted a twenty-eight pound gain in weight, cold hands and feet, and a chilly sensation over the whole body for the two years previous to the dispensary visit. There was a history of recent deafness, loss of hair, and dry skin. In addition she complained of dyspnea on slight exertion for the past two years. She stated that she could not

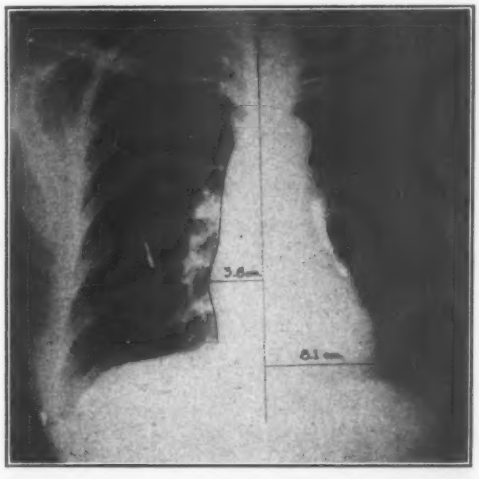

Fig. 12.—Teleroentgenogram of Case 5 after thyroid extract for ten weeks. Ml= 8.1; Mr=3.8; T=11.9. Diaphragm in Fig. 12 one-half interspace higher than in Fig. 11.

climb more than one-half flight of stairs without being compelled to stop for breath. This seemed to be the leading symptom on questioning her. Dropsy of the legs for six months was also complained of. She stated that she was mentally duller and slower of speech. She also complained of a choking sensation in the neck. On examination, the patient was seen to be drowsy and apathetic. Her face was swollen and round. The eyelids were swollen and the lid slits narrow. The lips were thick. The complexion was sallow with cyanotic patches over the malar areas. The lips were cyanotic. The hair was thinned out. The thyroid was enlarged and extremely hard. X-ray examination showed some tracheal compression. The skin was dry, scaly, and thickened. There were moist râles at both lung bases. The heart sounds were faint. There was shifting dullness in the flanks. The liver could not be palpated. There was some pitting edema of the lower extremities. The basal metabolism was −39 per cent. The blood pressure was 120/80 in the dispensary. In the hospital it was 100/65 on entrance. The pulse was 58. The urine showed albumin in faint traces at times but usually contained no albumin. The hemoglobin was 86 per cent; the red count was 4,200,000 on entrance to the hospital. The weight was 218 pounds. The teleoroentgenogram is shown in Fig. 9.

The patient was put on thyroid extract and in five weeks she had lost thirty pounds in weight, was mentally brighter, hearing was improved, the cyanosis had disappeared, the dyspnea was no longer present on such exertion as produced it when she was taken to the hospital. The ascites and edema of the lungs and lower extremities had disappeared. The blood pressure was 114/76; the hemoglobin was 82 per cent; the red count, 4,300,000.

The basal metabolism was plus 13 per cent on the last examination. The heart had been reduced 1.4 cm. in transverse diameter. (See Fig. 10.) Ligneous thyroiditis was diagnosed, and removal of a small amount of tissue to relieve the tracheal compression was advised, but the patient felt so well that this operation was refused and she went home after ten weeks in the hospital.

There can be no denying that in this case the definite subjective symptoms and objective signs of heart failure were due to the same cause as the myxedema, and disappeared when the myxedema disappeared following thyroid extract treatment. The decrease in trans-

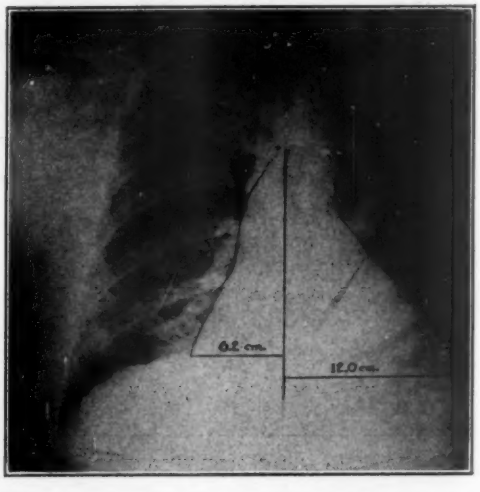

Fig. 13.—Teleroentgenogram of Case 6 before thyroid extract. Ml=12.0; Mr=6.2; T=18.2.

verse diameter of the heart after five weeks of thyroid medication is just beyond the errors of the teleoroentgenographic method as practiced here. We believe that the x-ray demonstrates a real reduction in heart diameter because the x-ray shown in Fig. 9 was checked by a similar film taken one week later and after one week of treatment. This film shows a heart only 6 mm. less wide than the heart taken one week previously. Fig. 10 was checked by a teleoroentgenogram taken two weeks earlier. This latter shows a heart 2 mm. wider than that shown in Fig. 13. This, it appears to me, proves that there was a definite dilatation previous to thyroid medication, with a reduction in transverse diameter of the heart of about 1.5 cm. after five weeks of thyroid extract treatment. The position of the diaphragm will not explain the reduction in size because the diaphragm was one-half in-

terspace higher in Fig. 10 than in Fig 9 and the higher the diaphragm, *ceteris paribus*, the greater the transverse diameter of the heart.

CASE 5.—A female, aged forty-six years, was sent into the University Hospital with the diagnosis "general edema, probably of heart origin." The chief complaints on entrance were shortness of breath of five years' duration gradually increasing in intensity; swelling of the ankles, more pronounced at night; hoarseness for three years; dizziness for five years; coldness of extremities for five years; poor memory for three years, gradually getting worse; slow and difficult cerebration; slow speech; dry skin and loss of hair for the past five years.

The patient had a swollen, expressionless face, sallow complexion with malar flush and cyanotic lips and finger nails. The skin was dry and thin, not typically myxedematous except over the fingers where the skin was thickened and strongly suggestive of the myxedematous condition. The heart was slightly dilated (T = 13 cm.) (Fig. 11). The heart sounds were faint. The second sound over the aortic area had a suggestion of the "hollow log" quality heard sometimes in atherosclero-

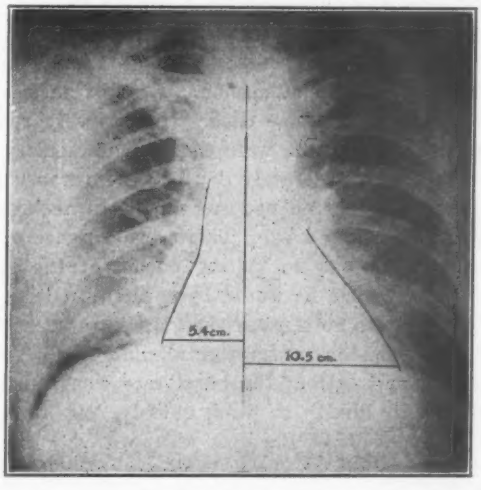

Fig. 14.—Teleroentgenogram of Case 6 after five weeks of thyroid extract. Ml= 10.5; Mr=5.4; T=15.4. Diaphragm slightly higher than in Fig. 13.

sis of the aorta as well as in luetic aortitis. The heart rate was regular, about 60. The lungs were normal. The abdomen normal. The patient was seen twenty-four hours after going to bed and there was no edema of the extremities at this time. The basal metabolism was −36 per cent. The blood pressure was 110/65. The hemoglobin was 70 per cent, the red count 3,900,000, and the white count was 6,800. The electrocardiogram showed an absence of T-wave in Lead I.

On thyroid extract the shortness of breath and the symptoms associated with myxedema disappeared. The teleoroentgenogram showed a diminution of 9 mm. in the transverse diameter of the heart after three and one-half weeks of thyroid medication. The patient has now been doing all her housework for six weeks since leaving the hospital, with no symptoms of dyspnea and no swelling of the ankles as was the case previous to medication with thyroid extract. Fig. 12 is a teleoroentgenogram of her heart taken ten weeks after Fig. 11, and after this patient had been at home for six weeks performing all her household duties without a symptom of cardiac insufficiency. The film reproduced in Fig. 12 reveals a transverse diameter of the heart 11 mm. smaller than in Fig. 11, with the diaphragm position both on the right

and left side about one-half interspace higher in Fig. 12 than in Fig. 11. Therefore, difference in diaphragm position cannot explain the decrease in transverse diameter of the heart, for it is such as to increase the diameter in Fig. 12. It is, of course, true that a difference of only 1 cm. in transverse diameter might possibly be due to variations in the technic of taking the teleroentgenograms. We cannot claim less variability than 1 cm. for the transverse diameter of the heart as the technic is carried out in this hospital. Yet we believe there actually was a decrease in transverse diameter of the heart under thyroid treatment for we had one other teleroentgenogram taken three and one-half weeks after medication was begun, and this showed a transverse diameter 9 mm. less than in Fig. 11. The T-wave became positive in Lead I of the electrocardiogram after thyroid treatment had been carried out for ten weeks. In this case the symptoms of heart failure were mild, it is true, and the dilatation of the heart was very slight, still these symptoms were definite and the dilatation was very probably present. On thyroid medication the symptoms of heart insufficiency disappeared and the dilatation of the heart was reduced 1 cm. in transverse diameter.

CASE 6.—A male, aged forty-nine years, entered the University Hospital with complaints of weakness progressively increasing for six years; yellow skin for five years; stubborn constipation for six years; shortness of breath on slight exertion increasing in severity for the past six years; swelling of hands, arms, feet and legs, first noticed one month previous to admission. Loss of memory and inability to think quickly had been noticed for some time. He was very sensitive to cold. On examination the most striking features were the loss of memory and the extremely slow cerebration. The skin was moderately dry but there was very little thickening. There was puffiness about the eyes and padding of the supraclavicular regions. The thyroid was just palpable and very hard. There was absence of vibration sense in both lower extremities. There was no pitting edema of the lower extremities on examination, though he stated that he would have pitting edema after being on his feet for long hours. There were no signs of heart failure excepting an enlargement (Fig. 13). There was no secondary anemia or albuminuria. The basal metabolism was −31 per cent. On thyroid extract the basal rate went up to +4 per cent, and the patient soon recovered his ability to think quickly, lost his apathy, the skin became normal and the puffiness about the eyes disappeared. The teleroentgenogram taken five weeks after putting him on thyroid extract shows a reduction of 2 cm. in transverse diameter despite the fact that the diaphragm is slightly higher both on the right and on the left (Fig. 14).

I have been following this patient in the dispensary for five months, and he is now working at easy jobs. His dyspnea on moderately severe exertion is very much less he states, but is still present. On slight exertion there is no dyspnea. There has been no return of pitting edema after long hours on his feet. There have been attacks of precordial pain on excitement on several occasions. The heart shadow now shows a slight reduction over that of Fig. 14, but there is still definite enlargement of the shadow beyond the limits of the normal for his height and weight. Apparently this patient had slight symptoms of cardiac insufficiency which largely disappeared after bringing his basal rate up to the normal. But there is still evidence of something wrong with his heart for the size is still beyond the normal limits. There have been symptoms suggestive of angina pectoris. The electrocardiogram shows no evidence for coronary sclerosis.

The blood pressure is normal and the patient has never had rheumatic fever or chorea. He had diphtheria six years before entering hospital and dates all his symptoms from this time. I think we are justified in the opinion that in this case of myxedema there were slight symptoms of cardiac insufficiency which largely disappeared when the basal metabolism became normal. There was also some reduction in the dilatation of the heart when the hypothyroidism disappeared. On the other hand, the heart size did not become entirely normal on thyroid treatment. There are still some residual symptoms of postdiphtheritic neuritis. It is a question whether the dilatation of the heart which is still present may be correlated with the previous diphtheria or with a coronary sclerosis. At any rate, there was some reduction in heart size after thyroid medication and the very mild symptoms of heart insufficiency have largely disappeared.

Case 1 has now been followed by me for four years. During all this time the patient has been largely free from all symptoms of myxedema and of heart insufficiency. At times she would become negligent with her treatment and then mild symptoms of myxedema with lowered basal rate would appear. At these periods heart failure symptoms would develop which would promptly disappear when she returned to her thyroid extract. Recently the patient returned for a careful study. It was then found that her blood pressure ranged around 200 mm. systolic and 100 diastolic, with the basal metabolism around +5 to +10 per cent. The blood pressure dropped somewhat on giving less thyroid, but with the basal rate around −5 per cent it is still approximately 170 mm. systolic and 90 diastolic. Moreover, the electrocardiogram now shows on every occasion a split and prolonged QRS group. The spread of the QRS group is now from 0.14 to 0.16 seconds. We have usually found such a split and prolonged QRS group associated with coronary arteriosclerosis of an advanced degree. Very occasionally such a QRS group seems to have no organic basis, but usually it is indicative of coronary disease. When Case 1 was first seen by us, a split and prolonged QRS group was present. This disappeared promptly on treatment with thyroid extract and at the time seemed of nonorganic basis. Approximately six months after putting the patient on thyroid extract the split and prolonged QRS group reappeared in her electrocardiogram and has remained constantly present despite a normal basal rate. Without an autopsy we can only speculate as to the basis of this QRS, but I am now inclined to believe that this patient had a certain degree of coronary sclerosis in 1923 when she first came under treatment. At this time the narrowing of the coronary vessels was very moderate. The split and prolonged QRS then appeared only because of insufficient circulation in consequence of the general retardation of minute volume which we

know is a feature of myxedema. When the circulation improved on thyroid extract treatment the split and prolonged QRS disappeared. Later as the vessels of the heart became narrower than they had been at the onset of treatment, a period was reached where the vessels were insufficient even with a normal minute volume and then the split and prolonged QRS reappeared. Only an autopsy can prove this speculation. At the same time there is a slight dilatation of the heart now present and very slight symptoms of cardiac insufficiency which I am inclined to believe are due to coronary sclerosis.

The patient reported as Case 2 is now seventy-two years of age and four years after beginning thyroid extract treatment shows not a sign of heart failure or myxedema. Coronary sclerosis may be present but there are no symptoms or electrocardiographic signs of it.

Case 3 has now been followed by me for one and one-half years. Two months after leaving the hospital the basal rate was + 6 per cent, the blood pressure 190/106 and the pulse rate 104. There was tremor of the fingers and the patient was very nervous. She was put on smaller doses of thyroid and the basal rate has been kept around – 3 to – 5 per cent. At this rate the blood pressure is 135/85. There are no symptoms of cardiac failure, the heart size is normal, and the electrocardiogram gives no evidence of coronary sclerosis. There is now no precordial pain.

Case 4 has not been heard from. Case 5 is in excellent condition. The follow-up of Case 6 has been reported above.

Until autopsy reports are available on these cases, it is idle to speculate much about the condition. We know that coronary sclerosis is not infrequently associated with myxedema, and it is barely possible that when there is a certain degree of coronary narrowing, heart failure develops when the minute volume of blood flow drops in consequence of myxedema. But why should the blood flow fall if the heart is sufficient? The blood volume is reduced in myxedema and marked reduction in blood volume leads to reduction in minute volume of the circulation. Possibly herein lies the secret of heart failure in myxedema. On the other hand, the skeletal muscles weaken very decidedly in myxedema. Where the basal metabolism is reduced we can expect the power of the heart muscle to be reduced. This may be part of the explanation of heart failure in myxedema. Perhaps the two factors, narrowed coronary circulation and reduced rate of oxygenation in the heart muscle in consequence of the hypothyroidism are sufficient for an explanation of heart failure in myxedema.

Christian,[12] Abrami, Brulé and Heitz,[13] and others have warned against the use of thyroid extract or advised great caution in its use in cases of myxedema complicated by angina pectoris. We believe that care and individualization in the use of thyroid extract must

be practiced. On the other hand, we have never yet had a case where thyroid extract was not of great benefit to the patient. In Cases 1 and 3 we saw reason to reduce the dosage because of hypertension, but only a very slight reduction was necessary to bring the blood pressure to nearly normal values. And, if the blood pressure would not come down to nearly normal without reducing the thyroid extract to the point where symptoms of myxedema would reappear, we would choose to have the high blood pressure without myxedema rather than this deplorable state with normal blood pressure. During a discussion of this paper at the Minnesota Academy of Medicine, Dr. Henry Ulrich stated that he had been called to see a case of mitral stenosis previously well compensated which had developed symptoms of heart failure and myxedema. He did not hesitate to give thyroid extract and the symptoms of heart failure disappeared. The symptoms of angina pectoris in coronary sclerosis are probably due to blood flow insufficient for the needs of oxidation in the muscle. Thyroid extract will increase the flow in cases of myxedema and coronary sclerosis, and in so far is of benefit. If exercise is taken this increased flow may be insufficient and angina pectoris may result. Not the thyroid extract but the increased activity is then the cause of the angina pectoris.

In none of our cases was the secondary anemia of such a degree as to be a determining factor in the heart failure. In fact the difference in the red count and hemoglobin before and a few weeks after treatment was negligible, at a time when the heart failure had disappeared. This does not mean that the secondary anemia plays no rôle in the heart failure. Given coronary narrowing and reduced rate of circulation in myxedema, the secondary anemia must aid in producing heart failure.

Only three of these six cases of myxedema had electrocardiograms taken both before and after treatment. In these three cases, 1, 2 and 5, there was a negative T in Lead I and a negative QRS group in Lead III before treatment. After treatment the T became positive and the left preponderance disappeared. A negative T in Lead I is usually associated with heart muscle damage where digitalis has not been given, and we believe that this electrocardiographic sign is additional good evidence that we frequently have heart muscle injury in myxedema.

CONCLUSIONS

Heart failure not very infrequently accompanies myxedema and disappears with the myxedema on treatment with thyroid extract. This heart failure is characteristic of myxedema as only thyroid extract will completely alleviate it. It therefore deserves the name of myxedema heart.

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THE PROGNOSIS AND TREATMENT OF THE RHEUMATIC INFECTION*

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THE widespread distribution of the rheumatic infection, its unparalleled importance as a cause of serious heart disease among children and young adults, and the resulting economic loss have created a growing appreciation of the grave problem which it presents. Despite this, the literature fails to emphasize sufficiently certain features that are of fundamental importance. It is not fully understood that, as an economic load upon the community, rheumatic infection ranks with tuberculosis and syphilis. Even the most superficial glance at the death rates in the registration area of this country during the past twenty-five years shows that deaths from heart disease considerably outnumber those from tuberculosis. Furthermore, while the tuberculosis death rate is steadily falling, that from heart disease is rising.

In 1890, Garrod[1] said, "The recurrent attacks of rheumatism differing so widely in their characters * * * present certain analogies with the phenomena of syphilis." Recently Swift[2] has emphasized the resemblance of rheumatic infection to syphilis and tuberculosis. There are points of similarity in the pathology. Chronicity, which is one of the outstanding features of syphilis and tuberculosis, is an equally striking character of rheumatism. In a great proportion of cases it extends over many years, presenting alternating periods of activity and apparent quiescence.

The study of the disease, however, is fraught with many difficulties. Its varied forms seem to extend from the most trivial "growing pains" to fulminating acute polyarthritis. To the frank acute rheumatic fever and chorea there have been added, gradually, a variety of clinical types, often trivial of themselves, and frequently not sufficiently well defined or characteristic safely to be regarded as specific. In one individual a single attack of acute follicular tonsillitis may usher in serious and progressive heart disease. Another may pass through repeated attacks and sustain no discernible damage to the heart, or present any of the phenomena which are associated with the varied picture of rheumatism.

In a previous paper, I have reported in detail a series of cases of rheumatic fever and chorea.[3] Certain of the outstanding features, however, warrant further emphasis. The significance of age in de-

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termining the guise in which rheumatism presents itself, the importance of age in the prognosis, the apparent relationship of chronic foci of infection, and the inherent chronicity of the rheumatic process, all have an important bearing on the handling of the individual case.

THE AGE AT ONSET

The age at onset of rheumatism is a factor in the production of the varied phenomena of the disease and in the prognosis. Its invasiveness appears in early to middle childhood, corresponding roughly to the termination of inherited immunity, and to the period of acquisition of the acquired immunities. At this time arthritis is relatively uncommon and mild. In its stead we find recurrent attacks of tonsillitis, the so-called "growing pains" of childhood, myositis, and other even more trivial complaints, which, in the light of subsequent knowledge, one is compelled to accept as probable evidence of rheumatism. In this age period, when the onset of the disease is so frequently insidious, the visceral phenomena, carditis, chorea, and subcutaneous nodules are more frequently encountered than at any other time. As one passes from the years of early childhood into the adult age groups, rheumatic infection is characterized by acute episodes of increasing severity. The less characteristic types, previously encountered, fall into the background, and involvement of the heart is less frequent. The migrating polyarthritis becomes the dominant phase.

In all but 10 of the 393 cases of rheumatic fever studied, and in all of the 89 cases of chorea, the age at the time of the first attack could be ascertained. Only 4.7 per cent of the cases of acute rheumatic fever occurred before the age of five, but thereafter the incidence curve progressively rises to a peak of 20.8 per cent in the group between ten and fifteen years. Throughout the succeeding half decades the

TABLE I

THE AGE AT ONSET

AGE (IN YEARS)	RHEUMATIC FEVER (CASES)	CHOREA (CASES)
0 to 5	18	1
5 to 10	61	52
10 to 15	80	29
15 to 20	53	7
20 to 25	47	
25 to 30	44	
30 to 35	24	
35 to 40	18	
40 to 45	10	
45 to 50	9	
50 to 55	6	
55 to 60 and over	13	
	383	89

curve slowly but progressively falls to 1.5 per cent between the ages of fifty and fifty-five years. No age group escapes, however, but the secondary rise in the final period is probably due to confusion with other types of arthritis rather than to a true increase in the incidence rate.

The grouping of eighty-nine cases of chorea, in similar fashion, emphasizes further the fundamental importance of the age factor. Before five years but one case occurred, and after passing the twenty year period, no primary cases were encountered. The peak of incidence is found between the ages of five and ten. Through the succeeding groups the curve falls rapidly.

CARDIAC INVOLVEMENT OF THE FIRST ATTACK

Just as the clinical type of rheumatism, and the frequency of occurrence, seem to vary characteristically at different ages, so the incidence of cardiac complications in the initial attack reflects again the importance of the age at onset. Individuals giving a history of diphtheria, scarlet fever, antecedent rheumatism or chorea were excluded from this analysis. Not all the cases included were seen in the first attack. Those observed for the first time in a later episode were included only if they were able to give a definite and precise statement as to the age at the time of the first attack and the presence or absence of cardiac damage at that time. Data derived from such a mixed group is naturally open to criticism, yet the error resulting is one which probably would tend to diminish rather than to augment the incidence of cardiac complications.

Those cases seen in the hospital during the initial episode were considered to have damaged hearts when any of the following conditions were found: definite valvular lesions, enlargement of the heart out of proportion to the degree of fever present, pericarditis, extrasystoles, or a persistently rapid pulse. Many of the cases, but not all, were studied by electrocardiogram, which has been shown to be an important and valuable means of determining the earlier and less severe forms of cardiac damage.[4] The failure to utilize this method in some of the earlier cases probably reduces the figure somewhat below the true incidence level.

Of the 366 cases of rheumatic fever analyzed, 250, or 68.3 per cent, showed evidence of cardiac disease at the time of admission or during their stay in the wards. Two hundred four of these were subsequently observed in the Follow-Up Clinic over varying periods of time, four months being the minimum. In 42 (20.6 per cent) the cardiac condition was definitely improved. Fifty-seven cases (27.9 per cent) presented evidence of a progressing lesion, and 51.5 per cent of the cases were found to be essentially unchanged.

Of 66 cases of chorea similarly studied, 34 (51.5 per cent) had

definite signs of cardiac involvement upon admission or during their stay in the hospital. Of the 41 cases followed after discharge, 11 (27.5 per cent) showed improvement in the cardiac condition, while 8 (19.5 per cent) had progressing lesions. Fifty-two per cent of this group were found to be unchanged.

The incidence curve of heart involvement in the initial attack of rheumatic fever approximately parallels that of the age at onset of rheumatism. Starting at 61.5 per cent in the group under five years, it reaches the peak between five and ten years, when 78.0 per cent are found to have evidence of cardiac complication in the first attack of acute rheumatism. It was only after the age of twenty-five that more than one-half of the primary cases escaped cardiac involvement. The secondary rises encountered in the two age groups,—thirty to thirty-five, and forty-five to fifty,—probably do not represent actual rise in incidence but are due, presumably, to the relatively small number of cases falling within these limits.

TABLE II

INCIDENCE OF HEART DISEASE IN THE FIRST ATTACK OF ACUTE RHEUMATISM

AGE	TOTAL CASES	CARDIAC INVOLVEMENT	INCIDENCE RATE (PER CENT)
0 to 5	13	8	61.5
5 to 10	41	32	78.0
10 to 15	58	43	74.1
15 to 20	33	21	63.6
20 to 25	31	19	61.2
25 to 30	36	15	41.6
30 to 35	20	10	50.0
35 to 40	16	5	31.2
40 to 45	11	3	27.2
45 to 50	7	3	42.9
50 to 55	4	1	25.0
55 to 60 and over	13	4	30.7

In the chorea series, however, the curve of heart involvement is a reversal of the curve of age incidence. While chorea most frequently makes its appearance between the ages of five and ten years, the occurrence of heart disease is less frequent than in any of the other groups. Between the fifteenth and the twentieth years, on the other hand, when the primary cases were found least frequently, the highest incidence of cardiac complications appeared. The small number of cases included, however, probably vitiates to a large extent the accuracy of these figures.

TABLE III

INCIDENCE OF HEART DISEASE IN THE FIRST ATTACK OF CHOREA

AGE	TOTAL CASES	CARDIAC INVOLVEMENT	INCIDENCE RATE (PER CENT)
0 to 5	0	0	0.0
5 to 10	36	15	41.6
10 to 15	18	8	44.4
15 to 20	4	2	50.0

The reports in the literature dealing with the frequency of heart involvement in the initial attack of rheumatism, vary within rather wide limits. In an analysis of 244 cases, Sir William Church[5] found that 75 per cent of the individuals under ten years presented signs of cardiac disease, and that, above this age, evidence of these complications progressively diminished to 12.5 per cent after forty. Poynton, Peterson and Spence[6] studying a group of children under twelve years, found the incidence to be 66 per cent in 172 cases of rheumatic fever and 44 per cent in 104 cases of chorea. In an analysis of 200 fatal cases of rheumatism, however, Poynton, Aggassiz and Taylor[7] found that of 100 who died under the age of twelve, 82 per cent had post-mortem evidence of acute carditis, while in a similar number above this age acute carditis was present in only 45 per cent.

The observations made in the Follow-Up Clinic after discharge from the hospital have an important bearing upon the treatment of these individuals after the subsidence of the acute phase of the disease. It was found that somewhat more than one-quarter of the rheumatic fever cases, and somewhat less than one-quarter of the choreas presented clinical evidence of a progressing lesion in the heart. This naturally raised the question of how prolonged a period of observation is necessary to ensure the final declaration of cardiac injury sustained during an acute attack of rheumatism.

Twenty-five cases, which were periodically examined after leaving the hospital, are illuminating in this respect. In them the development of mitral stenosis was observed. Twenty-two, or 88 per cent, showed well-developed physical signs of this condition within twenty-four months of the acute attack. Three of the cases, however, emphasize the tardiness with which this sequel may appear despite complete absence of subjective or objective evidence of active rheumatism. They were under relatively frequent observation, yet one of them showed none of the characteristic physical signs until after a lapse of five and a half years. The diagnosis was not made in the second case until six and a half years after the last active phase of rheumatism. The third, one of the chorea series, was observed for five years and eight months after the cessation of active disease before the mitral lesion became evident.

The prolonged period of time required for the development of mitral stenosis in these cases, despite freedom from evidence of active rheumatism, indicates that the disease process may at times remain clinically silent, yet slowly progress, inflicting further damage upon the heart. This concept is further supported by the not infrequent finding of Aschoff bodies in the myocardium years after the last clinical evidence of active rheumatic disease had disappeared.[8] It seems, therefore, that rheumatism may not only be active and chronic, but silent and progressive, over a very considerable period.

THE RÔLE OF FOCAL INFECTION

The belief that the disease, in some manner, depends upon infection has long been held; either that it is due to invasion by a specific agent, or that it depends upon a specific type reaction to nonspecific factors. This, and the frequent association of tonsillitis with acute rheumatic fever, carditis, and chorea has led naturally to the search for a responsible microorganism, and to the effort to eradicate all possible portals of entry. As yet the problem of the etiology remains unsolved.

The frequency with which acute tonsillitis appears just prior to, or during the onset of one of the active phases has led many observers into the concept of tonsillitis as an integral feature of the rheumatic syndrome. Linked with this, is the possibility that a chronic focus of infection might afford a *locus minoris resistentiae* for the entry of some specific organism, or play a significant part by reducing the general resistance of the individual. High hopes have been held that therapy directed along these lines might lessen the severity and abbreviate the duration of the disease. How well founded these hopes have been, it is still too early to ascertain with finality.

Reports in the literature are at variance. Kaiser,[9] in a study of two groups of school children, each 1,200 in number, concluded that tonsillectomy did not reduce the incidence of rheumatism, chorea, or heart disease. Ingerman and Wilson[10] in an attempt to ascertain the value of this procedure as a therapeutic measure, observed recurrence of rheumatism in 76 per cent of the cases operated upon, and in 80 per cent of the control group. Hunt,[11] reporting a similar study at Guy's hospital, London, found recurrences more numerous in a group subjected to tonsillectomy than in a larger group of unoperated controls. St. Lawrence,[12] however, concludes that tonsillectomy is a valuable procedure.

In this connection, it is important to emphasize that although the acute polyarthritis is usually a brief, and characteristically, a self-limiting phenomenon, yet the rheumatic disease underlying it is equally characteristically a chronic and often a silently progressing condition. The fact that only 50 per cent of the cases having subsequent acute attacks develop them within a period of three years after the initial acute rheumatic fever, necessitates a prolonged period of observation before the value of any therapeutic measure can be ascertained.

An attempt was made to control, to some extent, the observation on focal infection in this series, by studying the incidence in a group of 400 nonrheumatic cases similarly distributed throughout the arbitrary age periods. Certain striking contrasts were found. Definite chronic foci of infection were present in 317 of the 393 rheumatic fever patients, a total of 80.6 per cent in comparison with 67 per cent among

the control group. Infected tonsils were present in 231 (58.7 per cent) of the former, in contrast to 27.5 per cent in the control series. The relative incidence of other foci, however, was found to be quite uniform, with the exception of cervical adenitis which was considerably more frequent among the nonrheumatic cases. These findings appear to demonstrate that clinically evident foci of infection are more numerous among cases of rheumatic fever, and that diseased tonsils are more than twice as frequent in these cases as in a similar group of nonrheumatic patients.

TABLE IV

INCIDENCE OF FOCAL INFECTION IN THE CONTROL SERIES OF 400 CASES

	NUMBER OF CASES	INCIDENCE RATE (PER CENT)
Total cases having focal infection	268	67.0
Dental sepsis	157	39.2
Cervical adenitis	113	28.2
Tonsillar infection	110	27.5
Ears and nasal sinuses	6	1.5
Other foci	7	1.7

TABLE V

INCIDENCE OF FOCAL INFECTION IN THE RHEUMATIC FEVER SERIES

	NUMBER OF CASES	INCIDENCE RATE (PER CENT)
Total cases having focal infection	317	80.6
Dental sepsis	183	46.5
Cervical adenitis	33	8.1
Tonsillar infection	231	58.7
Ears and nasal sinuses	10	2.5
Other foci	7	1.7

The treatment of these foci, however, seemed to produce no great variation in the course of the disease. In addition to the removal of tonsils, when definitely indicated, all other available foci were treated. Eighty of these individuals were observed for an average period of three years and three months after the last attack of rheumatism; 34 (42.5 per cent) had recurrence of rheumatic fever. However, correction for the difference in the period of observation between the operated and unoperated groups, on the basis of the general incidence rate of recurrences, increases this figure to 48.9 per cent. Two hundred and seven cases, having no tonsillectomy or incomplete removal, were followed for a period averaging four years and five months. One hundred and twenty-five (60.3 per cent) suffered at least one return of the acute condition. However, the eradication of these foci is probably a wise and useful procedure provided that it is done during an inactive phase.

In general, a high incidence of chronic foci of infection and of tonsillar disease in particular, accompanies rheumatism. The correc-

tion of these abnormalities appears to be associated with a drop in the incidence rate of recurrence. The series is not sufficiently large nor is the time interval adequate in duration to justify any sweeping conclusions. A larger group must be studied over a period of five years or more before the rôle of focal infection can be determined and the value of the removal of chronic foci decided.

INCIDENCE OF RECURRENCES

That rheumatic fever tends to recur in many individuals after a longer or shorter interval is no new observation. Yet it is a fact which has been insufficiently emphasized. It is this characteristic, as much as the serious cardiac damage so frequently accompanying it, that makes prognosis so difficult, and it is this which leads to so much of the progressive disability.

Knowledge of the frequency of recurrence, and of the average time interval between the initial attack and the first recurrence is important. Recognition of the relationship between the age of the patient at the onset of rheumatism and the incidence of subsequent acute episodes is essential to the intelligent and proper management of the victim of rheumatic disease.

The figures presented here are based upon 252 cases, comprising only those individuals seen in the first attack of rheumatic fever, those who gave in the history an accurate date of the first attack, or those seen in the initial acute episode and followed in the clinic for at least six months after discharge from the hospital. Data of this sort cannot be accurate. The period of observation of patients seen in the initial episodes is entirely inadequate, as will be pointed out later, yet the figures are important since they unquestionably minimize the frequency of recurrences. Despite this source of error, however, it was found that 180, or 71 per cent, of this group of cases, irrespective of age at onset had at least one recurrence of acute rheumatism.

The age of the patient at the time of the initial appearance of acute rheumatic disease seems to play a further rôle in determining the frequency of subsequent episodes. When the cases are divided into an adult and a child group, with the age of twenty arbitrarily chosen as the dividing line, 51 of 87 cases comprising the adult group, or 58.6 per cent, had recurrences. Among the younger individuals, 165 in number, 129, or 78.2 per cent, had at least one subsequent attack of acute rheumatic fever.

TABLE VI

THE INCIDENCE OF RECURRENCE IN ADULTS AND CHILDREN

	NUMBER OF CASES	INCIDENCE RATE (PER CENT)
Adults, age group over twenty years	87	
Cases with recurrence in adult group	51	58.6
Children, age group under twenty years	165	
Cases with recurrence in child group	129	78.2

Furthermore, when the cases are grouped according to the age at onset, the striking frequency of recurrences among the younger patients is brought out again. The incidence peak is found among those whose first attack of acute rheumatism occurred between the ages of five and ten years. Of 45 children in this group, 42, or 93.4 per cent, had return of the acute phase. With two exceptions the curve after this age follows a steady downward course, but it is not until thirty that the incidence rate falls below 50 per cent. The secondary rises encountered in the two groups, twenty-five to thirty and forty to forty-five years, are due, probably, to the relatively small number of cases included. They emphasize, however, the fact that age does not confer immunity. With few exceptions those individuals who experienced two or more recurrences fell among the cases whose initial attack of rheumatic fever occurred within the first twenty-five years of life.

TABLE VII

RELATION OF INCIDENCE OF RECURRENCE TO AGE AT FIRST ATTACK

AGE AT FIRST ATTACK	TOTAL CASES	RECURRENCES	INCIDENCE RATE (PER CENT)
0 to 5	11	5	45.4
5 to 10	45	42	93.4
10 to 15	67	50	74.6
15 to 20	42	32	76.1
20 to 25	34	22	64.6
25 to 30	14	12	85.8
30 to 35	11	5	45.4
35 to 40	14	6	42.8
40 to 45	4	4	100.0
45 to 50	4	0	0
50 to 55	1	0	0
55 to 60 and over	5	2	40.0

The attempt to ascertain the average time interval between the initial acute episode and the first recurrence revealed a surprising fact. Only 56.8 per cent had the first recurrence within four years of the primary episode. Among the 144 cases available, 23.6 per cent occurred within one year, 38.8 per cent within two years, 52 per cent within three years, and 56.8 per cent within four years. Forty-three per cent of the cases waited four years or longer before the first secondary attack of acute rheumatism appeared. Apparently, therefore, it is only after a lapse of three years of complete freedom from symptoms that an individual has better than an even chance of escaping a further bout of acute rheumatic fever.

CHRONICITY

When a group of rheumatic patients is studied over a considerable period of time, the chronicity of the disease becomes strikingly apparent. Long intervals of freedom from obvious symptoms and signs, other than gradual progression of a cardiac valvular lesion which can

be explained adequately by damage sustained in a previous acute phase, may be abruptly terminated by a further attack of acute rheumatism. This is strikingly illustrated by the records of sixty-five cases from among those giving accurate histories, and others observed over a period of several years in the clinic and the wards of the hospital. Many of them have had recurrences of acute rheumatism after a period of ten years or more of apparent health and freedom from symptoms. There are scattered cases which show recurrences from fifteen to twenty-five years after the initial attack, and in four, acute rheumatism reappeared after thirty years.

Case 7 was a child six years of age at the time of the first attack of acute rheumatic fever; subsequent attacks developed ten, fourteen, nineteen and twenty-two years later. In Case 19 the patient had acute rheumatic fever first at the age of nine, a second attack eleven years later, and a third, thirty-one years after the onset. Case 26, a child ten years old at the time of the primary attack, had subsequent bouts wtih acute rheumatism five and twenty-eight years later. In Case 29 also the patient was ten years of age at onset, and developed rheumatic fever two, four, eight, and twenty-two years after. In Case 43, rheumatic fever occurred at the age of twelve and again after six, sixteen, and thirty-eight years. In Case 53 the patient developed the first recurrence after thirty-one years, and Case 57, after thirty-two years of freedom from symptoms of active disease.

Figures such as these give point to a question directed at a fundamental concept of rheumatic disease. Do these later acute attacks represent an exacerbation of a chronic but dormant process, in other words are they in the true sense of the word, recurrences, or do they represent reinfection? In the light of present knowledge it is manifestly impossible to give an unqualified answer. There are certain features, however, which incline me to the conviction that rheumatism is a truly chronic process. The frequency of multiple attacks of polyarthritis, the occasional individual exhibiting a persistent low-grade process extending over many weeks or months, with slight fever, leucocytosis, and mild and migrating joint pains, all point in this direction.

The scattered cases which survive an attack of acute rheumatism with little or no evidence of cardiac damage and yet, after a prolonged period of apparent freedom from activity, develop classic signs of mitral stenosis, emphasize the potential chronicity.

Probably the strongest argument that can be advanced at the present time is the pathological findings in the heart. If it be conceded that the Aschoff body is truly a specific rheumatic lesion, the presence of these nodules in cases coming to postmortem examination after many years of freedom from signs of active rheumatism must be accepted as strong evidence of the true chronicity of the disease process.

The delay with which final cardiac damage declared itself in some cases requires guarded prognosis and prolonged and careful observation of the patient. The frequency with which the morbid process in the heart progresses in the absence of any of the criteria of acute disease requires that this observation be careful and detailed, for serious permanent injury may follow upon a period of apparent quiescence, or of apparent minimal activity. The importance of repeated observations of the temperature, hemoglobin and blood counts, and weight curves of children, as well as the search for slight cardiac enlargement, tachycardia, and abnormalities of rhythm, cannot be overemphasized. When practicable, periodic electrocardiographic examination should be utilized in addition.

The wisdom of continuing salicylate administration to ambulatory and convalescent patients who are not under close supervision is questionable. That this group of drugs is of great value during the acute phase of the disease is undoubted. There is little or no evidence, however, to indicate that they have any direct effect upon the underlying pathological process. Their antipyretic and analgesic properties may, indeed, have a dangerous effect in masking evidence of renewed activity and in giving rise to a false sense of security.

The large group of children and young adults with definite cardiac damage present a special problem to the practitioner and to the community as a whole. To permit them to enter upon many of the common occupations, associated with considerable stress and strain, is essentially to saddle the community with their permanent care and maintenance after a varying period. The activity of the individual should be controlled by careful and prolonged observation and by repeated search for evidence of renewed activity. The victim of rheumatic cardiac disease requires careful consideration of his probable physical capabilities, and specialized vocational training.

Reference has been made to certain superficial analogies between this disease and the natural history of syphilis and tuberculosis. The latter require no emphasis as regards their economic importance; and this common feature has led to a broad and concentrated attack upon their inroads which has brought fruitful results in the form of arrest of progress and of cure.

Similarly, a study of the sequelae of rheumatism entitles it to serious consideration on the basis of its economic results alone. The cases seen in any large hospital fall roughly into two general groups. On the one hand is found a large number of individuals in the advanced stages of heart disease, usually before middle life, many of them with a fair prognosis as regards longevity, but destined, because of their handicap, to be a load upon the community. The second group is composed of younger patients with relatively mild, but none the less limiting, cardiac lesions, who, following a brief convalescence, are forced

to return to the severe competition of life without either adequate physical or educational resource to enable them to keep pace with their healthy contemporaries.

The community which has accomplished so much in the cure and the rehabilitation of the tuberculous patient, through the growth of sanatoria and the widespread dissemination of knowledge and propaganda, and in the intensive treatment of syphilis, has little or nothing to offer to the great number of individuals suffering from the sequelae of rheumatism until they become entirely incapacitated for further work. The failure, as yet, to discover the etiology has centered attention largely on this phase of the problem. Its true economic importance has tended to remain in the background, and little effort has been made to approach it from the point of view of long-continued therapy and rehabilitation by reeducation.

It is unfortunate that study of this important phase of the problem has fallen far behind the growth of knowledge of the varied clinical picture and pathology of the disease. A variety of drugs have been advocated and used. The technic of exhibition and the duration of the period of administration have varied within wide limits, with periods of enthusiastic belief that the fundamental course could be altered. Yet the conviction persists and grows that as yet our therapeutic armamentarium contains only drugs which afford a passing symptomatic improvement without altering the underlying and too often inevitable progress of the disease.

Two facts stand out from past experience in the treatment of rheumatism. Complete rest throughout the period of active disease is essential. Following this a prolonged and slow convalescence with fresh air, sunshine, proper diet, and limited activity have been found to give encouraging results.[13, 14]

These facts, and the clinical and pathological analogies existing between rheumatism and tuberculosis suggest a therapeutic approach which, as yet, has had but little, and that inadequate, trial. How much might be gained by prolonged treatment of the rheumatic patient along lines somewhat similar to the ideal sanatorium régime so successful in tuberculosis, it is impossible to foretell. That much might be gained, however, one is justified in believing a priori. Experience with children suffering from the effects of rheumatism has shown that, under the conditions of the cardiac convalescent homes where they are kept for an average stay of about eleven weeks, there occurs in most cases prompt gain in weight, improvement in hemoglobin and blood count, increase in cardiac reserve, as shown by exercise tolerance, and marked improvement in the general health.

With these facts in mind, and the concept of rheumatism as a chronic progressive disease, the time has come to investigate the value of prolonged sanatarium treatment in early cases.[15, 16] Experience

with convalescents, and certain of the fundamental characteristics of the disease indicate that such an experiment might well be attended by great benefit. It has been brought out that age plays a weighty part. In childhood the disease appears most frequently, is most often attended by serious heart involvement, and is followed more frequently by recurrences with their added menace. As puberty and adult life are reached, these features become less prominent. It is not unreasonable to believe that meticulous care of these young people under ideal conditions of surroundings, hygiene, and nutrition, might at least reduce the length of the active phase and delay the onset of recurrences sufficiently to carry the individual to an age when recurrences become less frequent and cardiac damage is less constant and less severe.

CONCLUSIONS

1. Rheumatism is a chronic and often a progressive disease characterized by alternating periods of activity and quiescence.

2. The age at onset seems to play a dominant rôle in determining the clinical phenomena, the incidence of cardiac involvement, and the incidence of recurrences.

3. Chronic foci of infection were found considerably more frequently in the rheumatic cases than in the group of 400 controls. Appropriate treatment of these foci seems to reduce but not to remove the incidence of recurrences.

4. Between the ages of five and ten years 78 per cent of the cases presented evidence of cardiac damage in the first attack. Only after the age of twenty-five does the incidence of heart disease fall below 50 per cent in the initial attack of rheumatic fever.

5. Seventy-one per cent of cases, irrespective of the age at onset of rheumatism, had at least one recurrence of the acute condition. Only 57 per cent of the first recurrences occurred within four years of the primary attack. This fact must be considered in the management of the patient and in the evaluation of any therapeutic or prophylactic approach to the problem of rheumatism.

6. Experience with convalescent cases suggests the possibility of mitigating the course of the disease by a modification of the prolonged sanatorium treatment which has proved so successful with tuberculosis. This has not as yet received an adequate trial.

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THE EFFECTS OF OUABAIN ON THE HEART IN THE PRESENCE OF HYPERCALCEMIA*

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NUMEROUS perfusion studies have shown that calcium in the perfusion fluid modifies considerably the action of digitalis on the heart.[1] The synergism between the two drugs, observed in these experiments, has proved to be of doubtful therapeutic value.[2] The fact that calcium may induce ventricular rhythms similar to those produced by digitalis led Edens and Huber[3] to examine the blood calcium content in patients particularly susceptible to digitalis bigeminy. They found the blood calcium values raised in many of these cases and concluded that this was a contributing factor in the increase in their susceptibility to the bigeminal rhythm. In a study of digitalis bigeminy, Gold and Otto[4] called attention to the fact that there are patients who are so susceptible that the bigeminal rhythm is induced before clinical improvement of the heart failure occurs. The question then arose whether the increased susceptibility to the bigeminal rhythm and to the fatal dose of the drug are simultaneous, or whether the two factors may be dissociated, a matter of considerable importance from the clinical standpoint.

The present study was undertaken to determine the effect of an increase in the blood calcium on the action of the digitalis bodies, more particularly to investigate (a) the effect of hypercalcemia on the susceptibility of the heart to the induction of idioventricular beats by the digitalis bodies, and (b) to determine the relation between a change in the susceptibility of the heart to idioventricular beats and a change in the fatal dose.

Eighteen experiments were performed on the dog. These are divided into the following three groups: (a) the effect of ouabain on normal dogs as controls, (b) the effect of ouabain on dogs with hypercalcemia resulting from the injection of calcium chloride, and (c) the effect of ouabain on dogs with hypercalcemia resulting from the administration of the parathyroid hormone (Collip). Freshly prepared solution of ouabain, 1:100,000, was injected by vein from a burette, usually about 5 c.c., every five minutes until death. In all cases electrocardiograms were taken before the ouabain injection was started, just before each successive dose, and as often between these intervals as seemed necessary. In some cases blood pressure tracings

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and carotid pulse pressure curves were also obtained during the various stages of the experiments. Blood serum calcium determinations were made by the Kramer and Tisdall method as modified by Clark and Collip.[5] Ether anesthesia was used for the operations in all except three of the experiments.

TABLE I

EFFECT OF OUABAIN IN NORMAL DOGS

EXPERIMENT	PERCENTAGE OF FATAL DOSE OF OUABAIN TO INDUCE IDIOVENTRICULAR BEATS	FATAL DOSE OF OUABAIN IN MG. PER KILOGRAM
3	67	0.108
5	60	0.125
6	64	0.178
8	63	0.117
17	40	0.123
19	57	0.114
	Average 58.5 per cent	0.1275 mg.

Normal Controls.—Table I gives the results of the ouabain injections in normal dogs. The average of six experiments shows that the fatal dose of ouabain for the normal dog by the method of injection used in these experiments is about 0.12 mg. per kilogram of body weight and that approximately 58 per cent of the fatal dose induces idioventricular beats.

Effect of Calcium Chloride.—Calcium chloride in 10 per cent solution was injected intravenously in doses varying from 10 mg. to 113 mg. per kilogram. These doses produced a marked fall in the blood pressure, frequently preceded by a slight transitory rise immediately after the injection. From the low level the pressure began to rise rapidly and within from ten to fifteen minutes after the injection it was either normal or somewhat higher. The electrocardiogram showed disturbance of the P-wave, QRS group, and T-wave, and with the larger doses ventricular tachycardia. These changes also disappeared almost completely within ten or fifteen minutes after the injection. In some instances a very small dose of ouabain reestablished these changes, showing in a striking manner certain points of similarity between the action of calcium and that of ouabain on the heart. Walters and Bowler[6] have shown that the intravenous injection of 82.5 mg. of calcium chloride per kilogram raises the blood calcium as much as 14 mg. per 100 c.c. blood above the normal and that from this level it gradually falls to normal in about four hours. In one of our experiments, thirty minutes after 100 mg. of calcium chloride per kilogram were given, the blood calcium was 20 mg. per 100 c.c. The results are given in Table II. Although there was no evidence from the electrocardiogram, the blood pressure or carotid pulse tracing, of a persistent calcium effect upon the heart, the fatal dose of ouabain

TABLE II

EFFECT OF OUABAIN ON DOGS HAVING PREVIOUSLY RECEIVED AN INTRAVENOUS INJECTION OF CALCIUM CHLORIDE

EXPERIMENT	DOSE OF $CaCl_2$ IN MG. PER KILOGRAM	PERCENTAGE OF FATAL DOSE OF OUABAIN TO INDUCE IDIOVENTRICULAR BEATS	FATAL DOSE OF OUABAIN IN MG. PER KILOGRAM
12	107	61	0.070
13	100	41	0.088
14	113	67	0.068
15	27	78	0.095
16	10	43	0.078
		Average 58 per cent	0.080 mg.

in these animals was only 0.08 mg. per kilogram and approximately 60 per cent of this dose was required to induce idioventricular beats. The injection of calcium therefore reduced the fatal dose as well as the dose necessary to induce idioventricular beats to approximately 60 per cent of that necessary to produce these phenomena in the normal animal.

Effect of Parathyroid Hormone.—The difficulty of producing persistent high blood calcium by the injection of calcium salts suggested the use of the parathyroid hormone which has been shown[7] to give rise to a hypercalcemia of considerable duration in normal dogs. It was also considered that the persistent high blood calcium might simulate more closely the conditions obtaining in the circulation of man in certain instances of disturbed calcium metabolism. The parathyroid hormone was given subcutaneously in several doses at intervals of about six hours. In five of the seven experiments the blood serum calcium ranged between 16.9 mg. and 25.6 mg. per 100 c.c. of blood. Five of the seven animals showed typical symptoms of parathyroid hypercalcemia of varying degrees: progressive weakness, vomiting, and depression of pain sensibility. The tissues were dry and the blood

TABLE III

EFFECT OF OUABAIN ON DOGS WITH HYRERCALCEMIA RESULTING FROM ADMINISTRATION OF PARATHYROID HORMONE (COLLIP)

EXPERIMENT	DOSE OF PARATHYROID HORMONE IN UNITS PER KILOGRAM	CONDITION OF ANIMAL BEFORE OUABAIN INJECTION	SERUM CALCIUM IN MG. PER 100 C.C.	PERCENTAGE OF FATAL DOSE OF OUABAIN TO INDUCE IDIOVENTRICULAR BEATS	FATAL DOSE OF OUABAIN IN MG. PER KILOGRAM
10	12	Sick	25.6	44.0	0.134
1	21	Very Sick	---	38.3	0.110
4	15	Normal	16.9	30.0	0.123
2	23	Very Sick	19.2	28.8	0.134
7	17	Normal	---	66.0	0.083
18	32.7	Sick	17.4	58.8	0.080
9	28.7	Very Sick	22.0	20.0	0.084

TABLE IV

SUMMARIZING RESULTS SHOWN IN TABLES I TO III

EXPERIMENTS	FATAL DOSE OF OUABAIN IN MG. PER KILOGRAM	PERCENTAGE OF FATAL DOSE OF OUABAIN TO INDUCE IDIOVENTRICULAR BEATS	FATAL DOSE OF OUABAIN DOSE FOR NORMAL IN PERCENTAGE OF FATAL ANIMAL	DOSE OF OUABAIN TO INDUCE IDIOVENTRICULAR BEATS IN PERCENTAGE OF DOSE NECESSARY TO INDUCE THEM IN NORMAL ANIMAL
Normals (6 animals)	0.127	58.5	---	---
Dogs with $CaCl_2$ (5 animals)	0.080	58	63.0	62.7
Dogs with Parathyroid Hormone				
Type I (4 animals)	0.125	35.3	98.4	60.0
Type II (2 animals)	0.082	62.4	64.5	69.1
Type III (1 animal)	0.084	20.0	66.1	22.7

of high viscosity. In one instance no more than 3 c.c. of serum could be obtained from 18 c.c. of blood. The effects of the hormone on the circulation have been described by Edwards and Page.[8] In the present series of experiments the electrocardiographic findings varied considerably in different animals. The first doses of the hormone generally brought on sinus irregularity or accentuated that already existing. This usually disappeared as the heart rate accelerated when the animal was caused to move about. There were disturbances in the pacemaker, the P-wave sometimes being upright, inverted, diphasic, high and low in the same lead. In a given lead the T-wave often showed similar variations. There were also varying degrees of impairment of conduction with S-A block, A-V block, and dropped ventricular beats. When the animal was made ready for the ouabain injection, the heart rate was generally quite rapid (150 to 180 a minute), though in one instance it was as low as 50 a minute due to sinus slowing combined with dropped ventricular beats.

From the standpoint of the manner in which the reaction to ouabain was affected in this series of experiments, there are three types of changes (see Table III). In the first group there are four animals in which the fatal dose was the same as the average normal, whereas the idioventricular beats appeared after about 35 per cent of the fatal dose. In the second group are two animals in which the reaction was the same as in those animals which had received calcium chloride, namely, the fatal dose was reduced to 64 per cent of the normal, and the dose necessary to induce idioventricular beats remained in about the same relation to the fatal dose as in the normal animal. The third type of reaction is represented by one animal in which the fatal dose of ouabain was reduced to 66 per cent of the average normal, whereas the dose necessary to induce idioventricular beats was only 20 per cent of the fatal dose. We have no data upon which to base a satisfactory explanation of the difference between the effect upon ouabain action, of hypercalcemia following the injection of calcium chloride and that following the parathyroid hormone. The latter produces certain effects not attributable to the hypercalcemia alone.[7] These may contribute to the change in response of the heart.

SUMMARY AND CONCLUSIONS

The results are summarized in Table IV. They show that:

1. There is marked synergism between calcium and ouabain on the heart and this may persist after electrocardiographic evidence of calcium action has disappeared.

2. Hypercalcemia increases markedly the susceptibility of the heart to the induction of idioventricular beats by ouabain.

3. In hypercalcemia produced by the injection of calcium chloride there is an equal increase in the susceptibility to the fatal dose of ouabain.

4. In hypercalcemia produced by the parathyroid hormone the fatal dose of ouabain may be either the same as for the normal animals or greatly diminished as in those having received calcium chloride.

5. The margin of safety between the fatal dose of ouabain and the dose necessary to induce idioventricular beats, while fairly constant in the normal animal, is not a fixed one. Under certain conditions the dose of ouabain necessary to induce both phenomena may be reduced to about the same degree. Under other conditions the fatal dose of ouabain may remain the same as for the normal, while the dose necessary to produce idioventricular beats may be much smaller than that for the normal animal, or the dose of ouabain to induce idioventricular beats may be diminished to a relatively greater degree than the reduction of the fatal dose.

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PREMATURE BEATS*

The Manner of Action Upon Them of Anoxemia, Raised Blood Pressure, Vagus and Accelerator Stimulation, Alkalosis, and Adrenalin

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THAT the appearance of premature beats varies as a result of certain extraneous factors has long been known, but the mode of action or the degree of influence of such factors has remained undetermined owing to the difficulty of enumerating a sufficient number of premature beats in human beings clinically and in animals experimentally.

I[1] have been able to determine that posture and exercise both have a definite effect in causing an increase in the number of premature beats in patients. It was found that whereas patients with evidence of arteriosclerosis often showed an increased number of premature beats in the post-deceleration period after exercise, those without this lesion as a rule manifested no such increase. It was also proved that the premature beat frequency was often increased together with a moderate increase in the pulse rate.

The object of the present work was to attempt to obtain evidence as to the factors possibly concerned in these very definite variations in premature beat frequency. The results obtained in the arteriosclerotic cases suggested that an inadequate supply of blood to some muscle area during exercise might result in a local anoxemia or in a local acidosis, and that these independently or in combination might suffice to explain the increase, by rendering the muscle more susceptible or by accentuating the local stimulus-producing mechanism.

RESULTS OF PREVIOUS WORK

Previous knowledge as to the effect of extraneous factors groups itself under two headings, variations in blood pressure and stimulation of cardiac nerves. Knoll[2] and Heidenhain found that a sudden increase in systemic blood pressure was not infrequently followed by premature beats, and this observation has since been sufficiently well substantiated. More recently Fredericq,[3] using the perfused turtle's heart, found that increased intracardiac pressure caused a greater excitability as shown by a diminished chronaxie. Premature ventricular beats are often increased by changes in posture,[1] and the

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effect of such sudden changes upon patients with paroxysmal tachycardia and premature auricular beats is well known. It is possible that here too the mechanism is primarily vasomotor, though the change is one of a fall rather than of a rise in systemic blood pressure.

The evidence concerning the effect of nerve stimulation is rather indefinite as regards the manner though not as regards the existence of the phenomenon. Rothberger and Winterberg[4] have produced ventricular paroxysmal tachycardia by simultaneous stimulation of both vagus and accelerator nerves in the dog, also[5] premature ventricular beats by accelerator stimulation of a heart previously affected by barium chloride. Kuré[6] produced in two animals premature ventricular beats by sympathetic stimulation, and Levy[7] by a sympathetic stimulation in the presence of chloroform. Lewis[8] produced short runs of ventricular paroxysmal tachycardia in a dog at one stage of an experiment by vagal stimulation, and Erlanger[9] during experiments on heart-block in two cases by vagal stimulation in the digitalized heart caused the appearance of several premature ventricular beats. Pressure upon the abdomen is known to inhibit an attack of paroxysmal tachycardia as well as premature auricular beats. Whether this mechanism is effective as a result of distending the auricle with blood, as Lewis[10] assumes, or whether it is caused by a depressor reflex through the vagus is open to argument.

Certain drugs are known to cause an increase or a diminution in the number of premature beats, both auricular and ventricular, by their local cardiac effect; adrenalin[11, 13] increases their number and quinidine[11] decreases it. The action of digitalis appears to vary. Coupling produced in the digitalized heart, when the auricle is fibrillating, is an example of increase in the number, but there is also evidence that seems to prove that in certain other conditions the reverse effect is shown.[11] Here again it is uncertain whether the change is one of muscle receptivity or of stimulus effectivity.

MECHANICAL CARDIAC FACTORS CAPABLE OF INFLUENCING PREMATURE BEAT FREQUENCY

Premature beat impulses, from whatever source, will only be effective in evoking a contraction of heart muscle during certain phases of the cardiac cycle; they will be ineffective during the refractory period and generally absent during the relative refractory period. The length of the refractory and of the relative refractory periods varies with rate,[14] vagal stimulation,[14] and the action of drugs. Also the degree of excitability is varied by the P_H,[15] probably by the oxygen saturation and by certain drugs. All or any of these factors, therefore, may be assumed to be effective secondarily in influencing the frequency of appearance of premature beats. Should the origin of the ectopic beats be parasystolic in nature any influence prolonging the refrac-

tory period will cause a diminution in their number, but should it be reentrant such prolongation might in some cases even cause an increase, though in others it will cause a decrease.[22] The effect of rate can be eliminated experimentally by driving the heart at constant speed, and that of vagal stimulation in shortening the ventricular refractory period can probably be discounted.[12]

A local factor is present in the revelation of premature beats, for, as pointed out by Lewis, hyperirritability alone is an insufficient reason; moreover, evidence for their localization is seen in the constancy to shape of the ectopic electrical curves in many patients during periods of years.

The explanation of an increase in premature beat frequency is presumably ascribable to earlier stimulus effectivity. The speed of their appearance, independent of the refractory period, must theoretically be governed by one of two factors, or by a combination of both. If *T T* (Fig. 1) be the usual threshold at which the local stimulus (*A E*) is effective in activating a premature contraction, and if

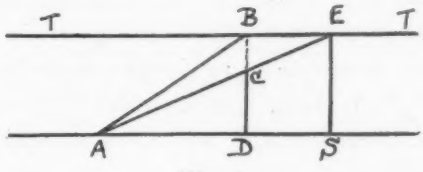

Fig. 1.

A S be the usual length of time necessary for this operation, then an earlier result at *D* will occur either because the threshold of activation is lower (*C D*) or because the rate of presentation of the same amount of stimulus (*B D*) is quicker (*A B*), the threshold *T T* remaining constant.

The following experiments were designed to try to determine which of these two results followed the interference of such extraneous factors as anoxemia, variations in blood pressure, vagus and accelerator stimulation, and variations in the blood reaction in the intact animal, and therefore in circumstances in some degree comparable to those obtaining clinically. In considering stimulus-material-formation it is of course necessary to include the delayed and possibly impaired stimulus of the reentry theory, a stimulus that is not so much autogenic as detached from the dominant rhythm.

The first series of experiments was designed for the purpose of evoking a number of electrically produced premature beats at a given threshold strength, and of determining the action upon the number of effective stimuli of the factors enumerated above. This is equivalent to measurement of cardiac excitability under conditions occurring in connection with premature beats in human beings. The

second series was an attempt to determine the effect of these same factors upon spontaneously occurring premature beats. Although the experiments were at first limited to ventricular premature beats, the auricular type was afterwards included as an additional check on the results, there being no reason to expect a difference in the mode action though the speed of the mechanism might very well vary.

METHOD

The animals used were dogs; the anesthetic was paraldehyde and ether, or morphine and ether. The chest was opened by a median incision, the sternum being split. The pericardium was incised, and its flaps anchored in such a manner as to give the best exposure of the right auricle and the anterior surface of the right ventricle and part of that of the left. Two pairs of stimulating electrodes were used. That for driving the heart at a constant rate was inserted into the anterior surface of the right auricle, that used for eliciting premature auricular or ventricular beats was inserted through the visceral pericardium into the auricular or ventricular muscle. The electrodes used were silver wire barbed needles, the stimulating electrode on the heart was the cathode on the break shock from an induction coil; the primary current for the premature beats came from a constant current storage batter of 4 volts, that for the regular driving stimulus from two dry cells. The strength of the secondary regular-stimulus driving shock was set at a level at which a regular rhythmic auricular response was obtained. The strength of the secondary current for evoking the premature beats was variable by means of the induction coil and a resistance in the appropriate primary circuit.

The two sets of stimuli were each obtained through electrically driven rotating contact makers. That for the driving shock had six contacts; that for the ectopic stimulus one, for each complete revolution. These contact makers were duplicated, the duplicate in each case being set slightly in advance, and being connected with the secondary circuits. In this way, the secondary make stimuli being short-circuited, only the break shocks were effective. The position of the premature beat-break stimulus was adjustable in time with reference to the subsequent regular stimulus. It was kept constant in each experiment and was placed as late in diastole as was practicable; this as a rule on measurement was after three-quarters of the cycle had passed, a distance, at the heart rates used, well removed from the relative refractory period. Thus, when every ectopic beat was effective runs of five normal auriculoventricular cycles would occur, followed by an auricular or ventricular premature beat. The anode of the driving circuit was a thick piece of German silver wire sewed on to the outer aspect of the pericardium; that of the premature beat circuit was similar in every particular to the cathodal electrode and was

inserted about half to three-quarters of an inch from it into the auricular or ventricular muscle. The heart rate was variable up to a rate of 200 beats per minute, and was set, as a rule, 20 beats per minute above the sinus rate. The opening in the thorax was covered by a plate of glass through which two holes gave access to the stimulating electrodes. A towel was wrapped under the glass to provide an additional guard against evaporation. The ventricular action was recorded by a Hürthle manometer attached to the carotid artery, and the auricular action by a lever attached by a thread and pully to the auricular stimulating electrode. The ectopic electrical stimulus was automatically recorded. The simple form of the irregularity made it possible to record it upon a large smoked-paper kymograph rather than by a string galvanometer; in this way both blood pressure and respiratory variations were also observable; moreover, tracings of considerable length could be obtained if necessary. After the inser-

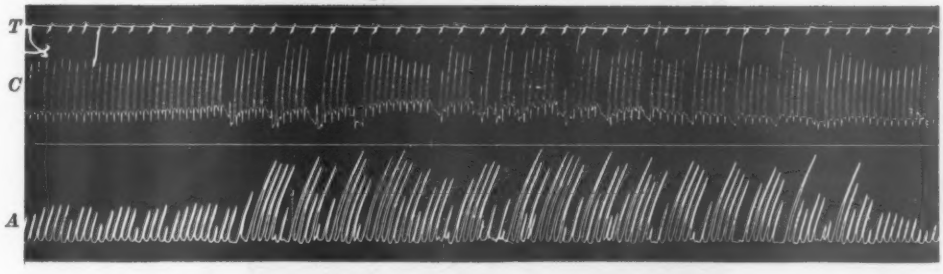

Fig. 2.—Subthreshold auricular premature stimuli become effective after the intravenous injection of 5 c.c. of adrenalin (1 in 500,000). The stimulus marking the ectopic shock is omitted, but the 1 in 6 response is sufficiently clear. In the middle part of the tracing there are several multiple responses. *C*, carotid tracing; *A*, auricular tracing; *T*, time in seconds; *S*, premature beat stimulus. (The relation of these four tracings is not a vertical one, but was determined for each experiment.)

tion of the electrodes a regular 1 in 6 in irregularity, shown to be due to premature beats, these being synchronous with the stimulating shock, was obviously the result of the 1 in 6 ectopic shock.

ELECTRICALLY PRODUCED ECTOPIC BEATS

The investigations were divided under two heads. Those at first performed were done in order to determine the effect upon local cardiac excitability of a number of different factors; those constituting the second class were performed in order to test the effect of the same factors upon the strength or rate of local spontaneous stimulus formation. In this way it was hoped that a clearer view might be obtained of the factors influencing the rate of premature beat appearance clinically.

The first series of experiments was performed as follows: The heart was driven, through the right auricle, at a constant rate. After every sixth regular beat a premature shock, auricular or ventricular,

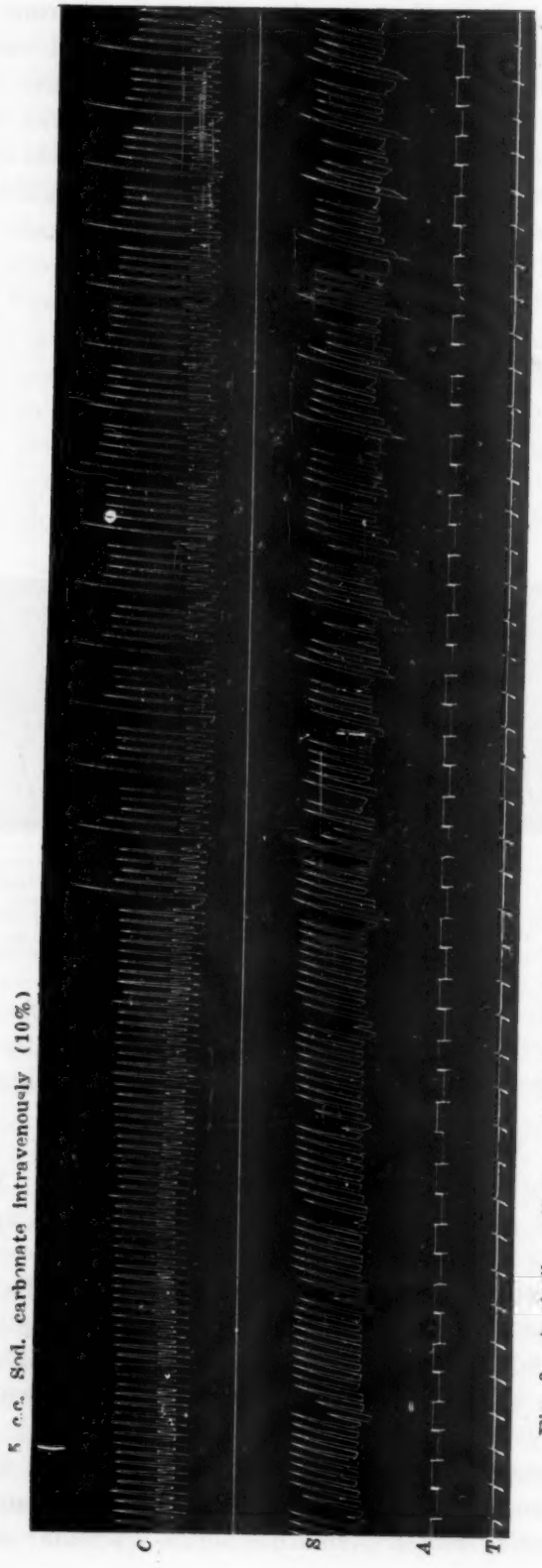

Fig. 3.—A similar effect resulting from the intravenous injection of 5 c.c. of a 10 per cent solution of sodium carbonate.

was interjected. The strength of the premature stimulus was then decreased until it was just not below the threshold of effectivity; thus, premature beats instead of appearing after every sixth, would appear after intervening intervals of 6, 12, or 18 beats. At this point the effect of anoxemia, increased blood pressure, vagal or sympathetic stimulation, alkalosis and acidosis was observed. The experiment was then several times repeated, conditions remaining unchanged, and finally the result at different stimulus strengths was observed. The strength of stimulus throughout each determination remained constant, and the result, therefore, gave the variation, if any, of the muscle receptivity, resulting from the particular added factor. The efficacy of the method is proved by the experimental result in the case of adrenalin, a substance known to increase cardiac excitability. Fig. 2 shows the increase of receptivity of the right auricle as a result of the intravenous injection of 5 c.c. of liq. adrenalin (1 in 500,000). This result was obtained with considerable regularity during the experiment concerned. An equally clear result was obtained by the production of a temporary alkalosis. (Fig. 3.)

THE EFFECT OF ANOXEMIA UPON RECEPTIVITY TO CONSTANT STIMULI

The effect of anoxemia was observed by rapidly cutting down the supply of air entering the lungs. The partial asphyxia was maintained until the systemic blood pressure became raised or until reflex hyperneic movements began.

Auricular Premature Beats.—Dog 11.—Four experiments were made over a range of stimulus strengths varying from that allowing only an occasional auricular premature beat to appear, about 1 in 30, to that allowing nearly 1 in 6. No increase or decrease in number was observed.

Ventricular Premature Beats.—Dog 1.—Four anoxemic experiments were made. There was no increase or decrease in the number of premature beats.

Dog 2.—One anoxemic experiment showed no increase or decrease in the number of premature beats occurring; the strength of stimulus was raised slightly above threshold.

Thus, anoxemia was not shown to have any effect in increasing or decreasing muscle receptivity to a constant stimulus in either auricle or ventricle. The importance of the evidence regarding the negative effect of anoxemia in the experiments concerned is increased, in the case of the ventricle, by the coexistent raised systemic blood pressure, which of itself might increase to some slight extent muscle receptivity to stimulation.

THE EFFECT OF INCREASED SYSTEMIC BLOOD PRESSURE UPON RECEPTIVITY TO CONSTANT STIMULI

Auricular Premature Beats.—Dog 10.—Six experiments were performed, the blood pressure being raised by pressure upon the abdomen. Three times there was no increase or decrease; on one occasion there was a slight increase, and on two occasions, the number of premature beats being nearly maximal, there was no decrease.

Ventricular Premature Beats.—Dog 1.—Of three experiments one showed no change as a result of increased systemic tension produced by abdominal pressure, and two showed a definite decrease in the number of premature ventricular beats arising during the period of raised pressure. After the pressure had fallen the number was again increased. The decreases were of the following order: (1) premature beats before the increased pressure 5 in 12 seconds; during increased

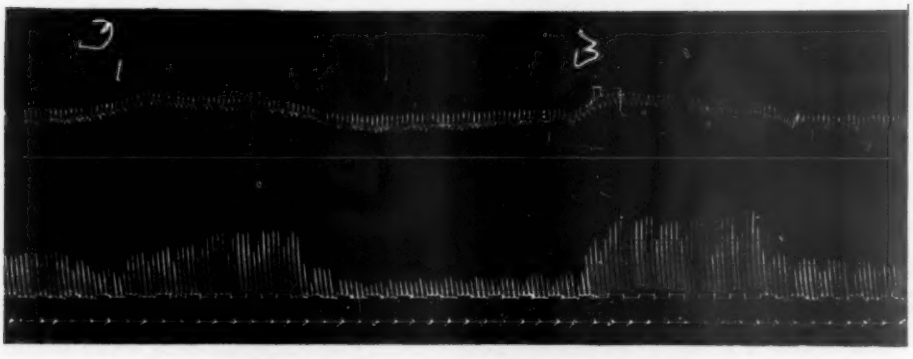

Fig. 4.—Variation in effectiveness of stimulation at a constant strength of ventricular muscle as a result of increased systemic tension.

pressure, none in 12 seconds; after increased pressure, 5 in 12 seconds. (2) The premature beats before the raised tension were 4 in 9 seconds, during it, 2 in 9 seconds, and after, 5 in 9 seconds.

Dog 2.—One experiment showed no change when the systemic pressure was raised by abdominal pressure.

Dog 3.—The pressure was raised three times by constricting the aorta. On all three occasions there was no change in the degree of stimulus receptivity. The tension was also increased twice in this animal by pressure upon the abdomen. On neither occasion was there any increase or decrease in the number of ventricular premature beats.

Dog 4.—Compression of the aorta twice produced a diminution in the number of ventricular premature beats and once had no effect.

Dog 6.—The systemic pressure was raised five times; the premature beats were slightly diminished three times, increased once, and once were not changed.

Dog 12.—On increasing the systemic pressure by abdominal pressure, the stimuli became effective towards the end of the period of raised tension on each of five occasions, there being in the intervals no effective stimuli. (Fig. 4.)

There is thus no evidence suggesting that increased systemic pressure causes an increased or decreased auricular receptivity to stimuli of constant strength. There is some evidence, though not very definite, suggesting that ventricular receptivity to constant stimuli may be changed during a temporary increase in systemic blood pressure. Tracings like that of Dog 12, where premature beats were only present during periods of increased pressure and absent between these, make the relationship likely.

VAGAL STIMULATION

Auricular Premature Beats.—The vagus stimulated was the left except in the case of Dog 6 (ventricular premature beats) in which case it was the right.

Dog 10.—Throughout this series of experiments the stimulus strength was increased from a point at which no ectopic beats appeared to one at which 1 in 6 was effective; the strength was then again reduced to a minimum. Seventeen determinations in all were made at the different levels of stimulus strength. No evidence was obtained that vagal stimulation caused any increase or decrease during the stimulation which was of a strength sufficient to cause slowing in the autonomous heart.

Dog 12.—Five experiments were performed, the results in all cases being negative.

Dog 14.—Three experiments showed no change in premature beat frequency during vagal stimulation; after all three for a period of 20 seconds the premature beats were fewer in number.

Ventricular Premature Beats.—Dog 2.—Vagal stimulation was at a strength sufficient to produce auriculoventricular standstill. In fifteen experiments there was seen no increase or decrease in the number of effective premature beat stimuli, the strength of stimulus being varied from that sufficient to produce a complete 1 in 6 response to that allowing only an occasional response. On certain occasions, although there was no change for less than 10 seconds after the end of stimulation, there was an increase between about the tenth to twentieth second afterwards. It is questionable whether this delayed effect is significant, particularly as it was by no means invariable.

Dog 3.—Vagal stimulation was at a strength sufficient to cause slowing of the autonomous heart, and was maintained for from 5 to 10 seconds. There was no change in the driven heart during vagal stimulation or after it in eleven experiments; one showed a definite

increase in the number of premature beats, a 1 in 12 ratio falling temporarily to 1 in 6.

Dog 4.—Vagal stimulation was at a strength sufficient to cause slowing of the heart. In eight experiments there was no change in premature beat frequency during vagal stimulation; immediately afterwards there was no change four times and four times there was an increase in the number of premature beats.

Dog 6.—There was an increase in the number of premature beats during vagal stimulation in two cases, and no change in three. After vagal stimulation there was no change in four and an increase in one case.

Dogs 3 and 6.—Vagal stimulation was on three occasions accompanied by an increase in the effectivity of the ectopic stimuli. Only experiments in which the 1 in 6 ratio was clearly maintained were counted, other pauses in the ventricular tracing being possibly accountable for by ventricular standstill. It is possible, therefore, that some positive results have been omitted. There is thus some evidence that vagal stimulation may in some cases increase the receptivity of the ventricular muscle to stimuli of constant strength.

ACCELERATOR STIMULATION

The left inferior cervical ganglion was exposed in every case, and the branches from it that encircled the subclavian artery were isolated. The particular branch used for the experiments was the one found in the individual animal to give acceleration and augmentation in the undriven heart.

Auricular Premature Beats.—Dog 11.—The stimulus strength was varied thirteen times from that sufficient to evoke an ectopic beat every time (i.e., after 6 regular beats) to that insufficient to produce more than occasional response. During this experiment there was no evidence that accelerator stimulation produced an increase or a decrease in the auricular receptivity to stimuli of constant strength.

Dog 12.—Five experiments gave equally negative result.

Dog 13.—Eighteen experiments gave negative results.

Ventricular Premature Beats.—Dog 5.—Accelerator stimulation on nine occasions produced no effect after the appropriate latent period; on two occasions there was a diminution in the number of ventricular premature beats. During stimulation there was on nine occasions no change, once an increase, and once a decrease in the number.

Dog 8.—After the latent period there was on five occasions no change, on one occasion an increase, and on one a decrease. During stimulation there was on two occasions an increase and on five occasions no change in the number of premature beats.

Dog 9.—After the latent period accelerator stimulation on nine occasions produced no change and on three an increase in the number of ventricular premature beats.

It would appear that the receptivity of auricular and ventricular muscles to stimuli of constant strength is not increased or diminished by accelerator stimulation.

ALKALOSIS AND ACIDOSIS

Alkalosis was produced temporarily by the intravenous injection of 5 c.c. of a 10 per cent solution of sodium carbonate. The increase in pulse-pressure[16] usual to this measure followed after a short latent period generally of about 15 seconds, and became maximal after an equal length of time. The tachycardia that also results in the undriven heart was excluded by maintaining a driven rate of about twenty beats per minute above that of the sinus. In both auricle and ventricle evidence was obtained that there resulted a definite lowering of the threshold of receptivity to a constant stimulus (Fig. 3). In the auricle the results were very clear, the time of appearance of the premature beats being nearer to or further away from the time of injection according to whether the ectopic stimuli were immediately or a little further below threshold strength. The results in the case of the ventricle were positive but less clearly marked. (Fig. 5.)

Auricular Premature Beats.—Dog 14.—Five cubic centimeters of sodium carbonate were injected intravenously. Premature beats were definitely increased on two occasions.

Dog 15.—Two experiments were performed; one showed a definite increase in the number of effective stimuli, one showed no increase but the strength of stimulation was here well below threshold.

Dog 17.—Five positive results were obtained (Fig. 3).

In every case the premature beats became increased after the initial augmentor effect had nearly reached its maximum. That the increased tension was not concerned in their appearance is proved by the negative results obtained upon raising the systemic blood pressure in previous experiments; moreover, it is difficult to see how such an increase in tension could affect the right auricle. The emergence of the premature auricular beats was earlier in proportion to the nearness to threshold of the constant stimulus, as judged by the number of premature beats appearing before the injection. The intravenous injection of 5 c.c. of 1 per cent lactic acid produced inconclusive results. It was difficult to determine whether premature auricular and ventricular beats were increased, diminished, or unaffected by it.

Ventricular Premature Beats.—Dog 8.—In five cases there was an increase in the number of ventricular premature beats after the intravenous injection of 5 c.c. of a 10 per cent solution of sodium carbonate.

Fig. 5.—Subthreshold ventricular premature stimuli become effective after the intravenous injection of 5 c.c. of a 10 per cent solution of sodium carbonate; the stimulus produces a double ventricular ectopic response.

Dog 7.– Four times intravenous injection of sodium carbonate was followed by an increase, stimulus strength being constant. There were two negative results, the threshold possibly being temporarily too high.

Dog 17.—Four positive results were obtained and two negative. The positive were identical in time relationship to the auricular results but were not so prolonged. (Fig. 5.)

It is thus clear that the receptivity of both auricular and ventricular muscle to stimuli of constant strength is enhanced by the temporary alkalinity produced. The effect was most clearly seen in the case of the auricle, this structure throughout the investigations being apparently most sensitive to all factors employed.

THE EFFECT OF ADRENALIN

Dog 18.—The receptivity of auricular muscle to stimuli of constant strength was shown to be heightened after the intravenous injection of adrenalin. The effect was present after injection of 5 c.c. of 1 in 1,000,000 solution, and was well marked after the injection of 5 c.c. of 1 in 500,000 solution (Fig. 2). This experiment was performed in spite of the fact that adrenalin is already known to heighten excitability,[20, 21] in order to give a result to which the other results, negative and positive, could be compared. Incidentally since accelerator stimulation appears by this method not to heighten receptivity, it is demonstrated that the adrenalin effect is not only a peripheral one upon the cardiac sympathetic endings, but also one upon the heart muscle itself.

In the case of ventricular muscle the results were less constant and were obtained at a lower dilution. In Dog 19 of ten experiments three showed no change in receptivity; seven results were positive, showing an increase in the number of ventricular premature beats after the injection in the case of three of the experiments, in which a dilution of 5 c.c. of 1 in 500,000 solution was used, and in the case of four in which the dilution was 1 in 200,000. In Dog 20, of eight experiments, six were positive and two were negative. The dilutions were from 1 in 300,000 to 1 in 200,000.

AUTOGENIC PREMATURE BEATS

The investigation of the reaction of anoxemia, raised systolic tension, vagal and accelerator stimulation, and alkalosis upon autogenic ectopic stimulus formation on the part of the auricular or ventricular muscle is complicated by the comparative rarity of these irregularities in the dog's heart under experimental conditions. The following observations were collected by seizing what opportunities happened to arise during the course of the first group of experiments; and, in addition, by attempting to cause the appearance of the irregularities

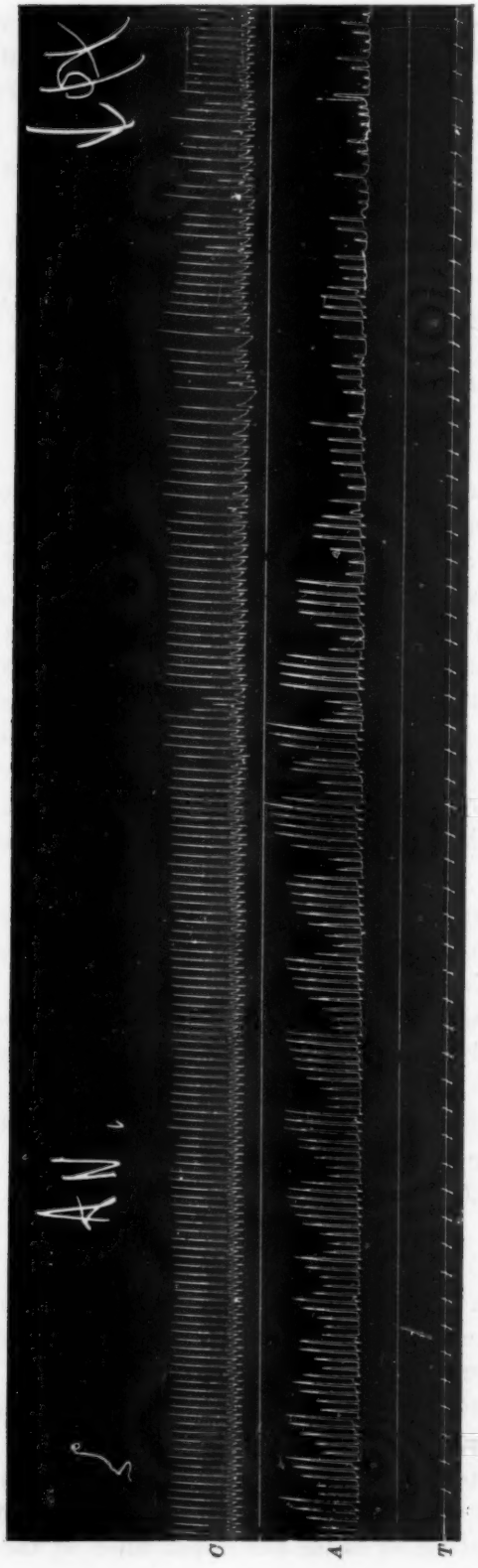

Fig. 6.

Figs. 6 and 7.—Autogenic premature auricular beats and premature ventricular beats become more frequent during periods of anoxemia.

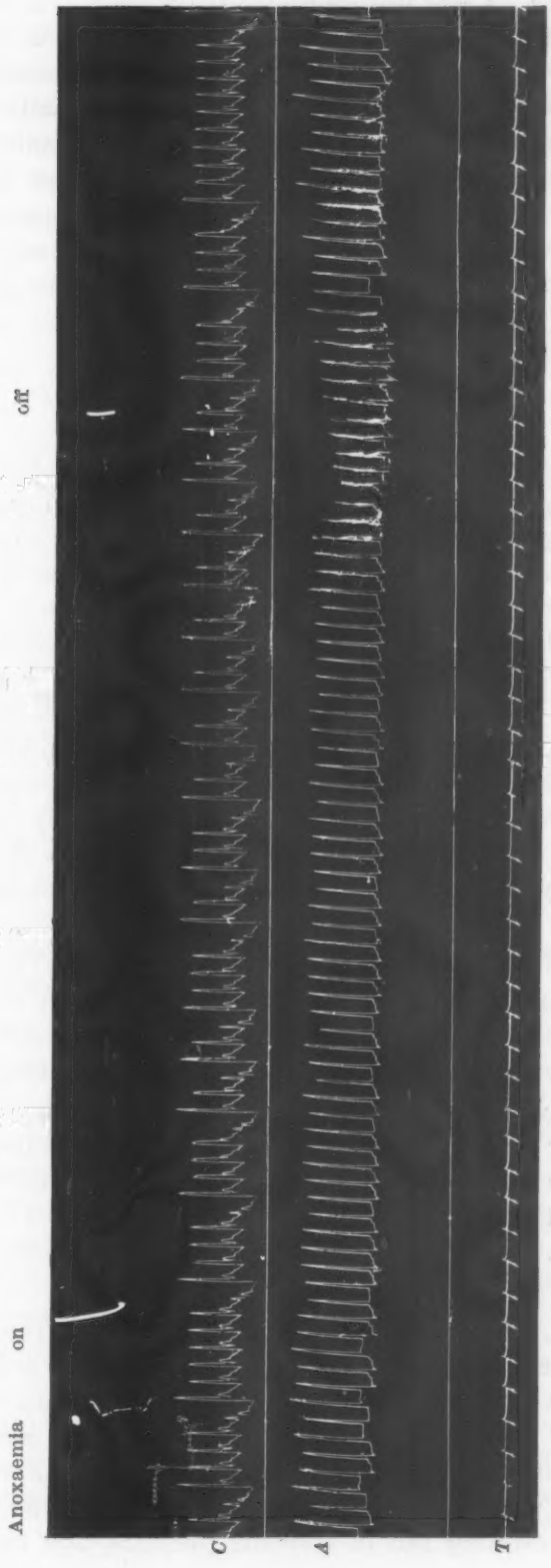

Fig. 7.

by various means. Local injection into the muscle of a few drops of barium chloride, 0.5 or 1 per cent, and ligation of a branch of a coronary artery were the most effective means. The insertion or the presence of the auricular electrodes seemed occasionally to be sufficient to initiate premature auricular beats; not infrequently the abnormalities appeared apparently spontaneously, though there is little doubt that they were even then due to adventitious causes, mechanical, manipulative, anesthetic or toxic. Whatever the cause, the stimulus to which the heart responded was autogenic. The smaller number of the results obtained is compensated for by their being largely positive rather than negative.

ANOXEMIA

Spontaneous Auricular Premature Beats.—Dog 14.—About half way through the experiment a number of premature auricular beats appeared, singly and in runs of 2 or 3; the heart at the time was being driven, the auricle in addition was receiving an electrically ectopic stimulus after every five regular beats. The presence of runs of premature beats suggested a spontaneous as well as an electrical factor, and both types of stimuli were therefore stopped. A few premature auricular beats still appeared spontaneously. On producing a temporary anoxemia the number was greatly increased, singly and in one run of 3 together (Fig. 6). On restoring normal respiration they again became much less frequent without completely disappearing. Change in rate does not account for their appearance for the rate is actually slightly higher at the end of the tracing than at the beginning.

Spontaneous Ventricular Premature Beats.—Dog 15.—After completing the usual preliminary operative technic a number of ventricular premature beats appeared spontaneously. Anoxemia caused a marked increase in their number, afterwards they became considerably fewer.

Dog 16.—A ligature was placed around the midpoint of the anterior septal coronary branch. A large number of ventricular premature beats appeared; anoxemia in three instances caused a definite increase in the number (Fig. 7).

INCREASED SYSTEMIC BLOOD PRESSURE

Spontaneous Auricular Premature Beats.—Dog 3.—Toward the end of the experiment a number of spontaneous auricular beats appeared. Raised systemic blood pressure produced a definite diminution in their number during the raised tension on six consecutive occasions (Fig. 8). This experiment was a preliminary one, and only a mercury manometer tracing was made, but the position of the premature beats is shown by the resulting fall in systemic pressure, and their auricular

nature was clear to the eye; the premature flick of the auricular contraction was seen to precede the ventricular movement each time. The decrease in their number was caused by tightening a ligature about the abdominal aorta, and the effect on the auricular premature beats must therefore have been due to some other cause than that of distention of the auricle by blood as suggested by Lewis[10] in the case of pressure upon the abdomen. It was conceivably produced by a reflex mechanism, possibly a vagal one.

Spontaneous Ventricular Premature Beats.—Dog 13.—Premature ventricular beats were produced by intramuscular ventricular injection of a few drops of a 0.5 per cent solution of barium chloride. There was an increase in their number during one of two occasions upon which the systemic pressure was raised.

Dog 17.—Premature ventricular beats resulting from ligature of the anterior septal coronary branch were on two occasions increased with the rise in systolic pressure produced by pressure upon the abdomen.

No investigations were made with the special object of determining the effect of increased systemic blood pressure upon spontaneous ventricular premature beats since the resulting increase in their number is already sufficiently well known.

VAGAL STIMULATION

Spontaneous Auricular Premature Beats.—Some spontaneous auricular premature beats occurring in Dog 17 during the experiment were abolished twice by vagal stimulation and twice were unaffected. The known inhibitory effect of vagal stimulation upon paroxysmal tachycardia is a homologous phenomenon.

Spontaneous Ventricular Premature Beats.—Dog 14.—Vagal stimulation twice, during the appearance of a considerable number of ventricular premature beats resulting from ligation of the lower part of the anterior septal coronary branch, produced no decrease and no obvious increase in their frequency.

Dog 17.—Ventricular premature beats appeared spontaneously in this animal during a period of several minutes. The vagus was stimulated twelve times at a strength just insufficient to produce slowing. On six occasions premature beats occurred during the period of stimulation. In the considerably longer intervening periods they only arose three times.

There would thus seem to be some probability that vagal stimulation diminishes the number of auricular premature beats and increases that of ventricular premature beats when these irregularities arise spontaneously in the heart.

ACCELERATOR STIMULATION

Spontaneous Auricular Premature Beats.—Dog 13.—Some spontaneous auricular premature beats appeared in the course of the experiment. Twice their number was definitely increased after accelerator stimulation, and on one of these occasions a short period of auricular flutter resulted (Fig. 9). The heart in this experiment was not poisoned in an way, as in the cases of Rothberger and Winterberg and Levy; moreover, the premature beats were auricular, not ventricular.

Dog 16.—Auricular premature beats appeared only after accelerator stimulation on three occasions, there being no sign of them in other parts of a tracing of an experiment lasting three hours.

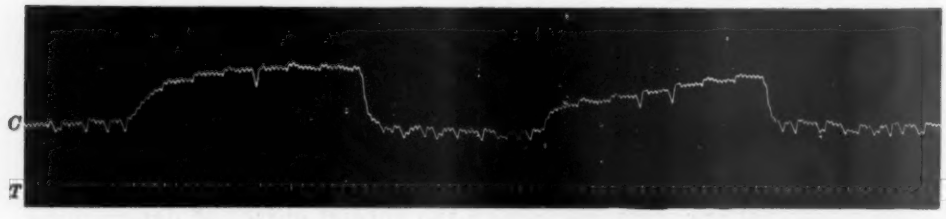

Fig. 8.—Decrease in spontaneous auricular premature beats during rises in systemic pressure.

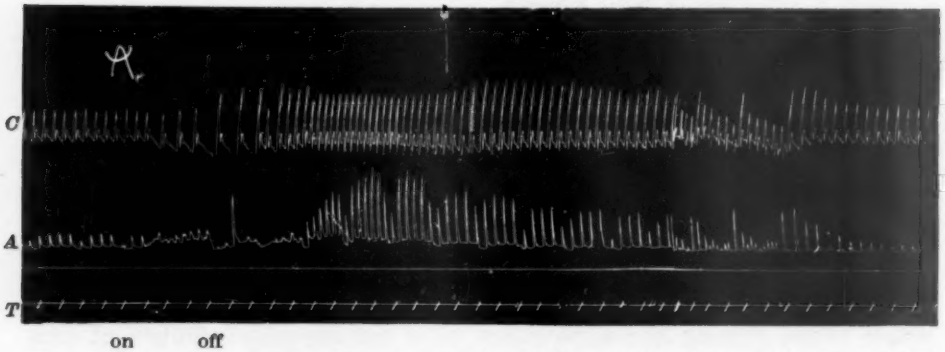

Fig. 9.—Two short paroxysms of auricular flutter (rate about 340 per minute) appeared after accelerator stimulation.

Ventricular Premature Beats.—Dog 11.—After the intravenous injection of a few drops of a 1 per cent solution of barium hydroxide premature ventricular beats appeared; they were increased in number six times after accelerator stimulation.

Dog 13.—After the intramuscular injection of a few drops of barium chloride, 0.5 per cent, a number of ventricular premature beats appeared. They became more frequent in number four times after accelerator stimulation.

Dog 16.—Ventricular premature beats were produced by ligating the anterior septal coronary branch. Accelerator stimulation produced an increase in their number on thirteen occasions (Fig. 10). Their

appearance corresponded each time to that of the maximal augmentor effect.

It is thus clear that accelerator stimulation increases the rate of production in both auricle and ventricle of premature beats when they rise as a result of processes occurring in the heart muscle itself.

THE EFFECT OF ALKALOSIS

Spontaneous Auricular Premature Beats.—Dog 14.—Some spontaneous auricular premature beats made their appearance towards the end of the experiment. Their number was considerably increased after the administration of 5 c.c. of a 10 per cent solution of sodium carbonate. This was in the undriven heart, no electrical stimulus being applied. The rate before and after was unchanged, though the cardiac output was considerably increased, there being a raised systolic pressure and a lowered diastolic, the mean blood pressure being

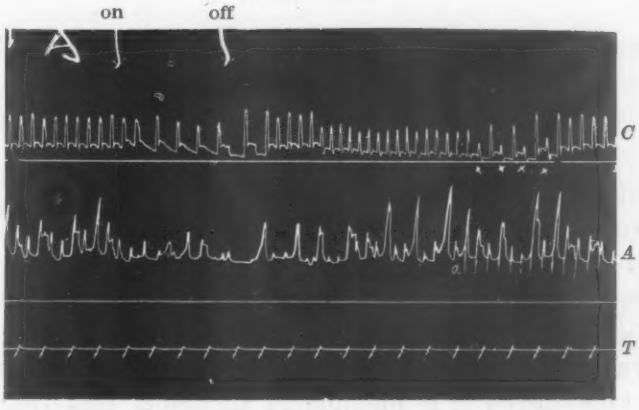

Fig. 10.—Autogenic ventricular premature beats were increased in number after accelerator stimulation.

slightly raised. It is conceivable that the increased auricular systolic force that resulted was a factor in their spontaneous appearance. Since alkalosis has been shown to lower the threshold of auricular muscle to stimuli of constant strength there is no evidence to prove in this experiment an increase in the activity of local stimulus formation.

Spontaneous Ventricular Premature Beats.—In Dog 14 twice and in Dog 17 twice spontaneous ventricular premature beats were increased in number after the intravenous injection of 5 c.c. of a 10 per cent solution of sodium carbonate intravenously. Two factors make it impossible to draw a correct deduction from this finding: first, the increase of systemic blood pressure which is known to influence the currents of the abnormality as it occurs spontaneously, and second, the fact that alkalosis has been shown to lower the threshold of ventricular receptivity to stimuli of constant strength. There is thus no

evidence to show that alkalosis causes an increase in the number of ventricular premature beats when they rise spontaneously as a result of an inherent cardiac mechanism. In so far as the number is in both cases increased it is probable that alkalosis does not inhibit the local mechanism in either auricle or ventricle, and possible that it increases its activity. Some of the findings of Andrus and Carter[19] are suggestive.

ADRENALIN

The effect of adrenalin in causing the appearance in the toxic and even the normal heart of premature beats, both auricular and ventricular, is too well known to require more than a reference. The fact that the irregularities appear de novo, and not merely at an increased frequency, is sufficient proof that local ectopic stimulus production is much enhanced, in addition to the increased muscle excitability that occurs.

DISCUSSION

Since some of the changes produced in the intact animal as a result of the experimental measures above described are multiple, it is necessary to analyze them at further length, before definite conclusions can be drawn as to their exact interpretation.

Anoxemia.—Other results, besides oxygen lack, are a raised systemic pressure and an increase in both vagal and accelerator tone. The muscle receptivity to stimulation is apparently unaffected by any one of these three phenomena. Spontaneous auricular premature beats are, if anything, inhibited both by raised systemic blood pressure and by increased vagal tone. Though they are increased in number by accelerator stimulation it is possible in anoxemia that there may be a sufficient increase in accelerator tone for this to be a factor in their more frequent appearance. Spontaneous ventricular premature beats appear to be increased in number by a raised tension and increased by accelerator stimulation. In several of the experiments in which an increase in their number followed anoxemia, there was practically no increased tension. It is therefore safe to infer that the effect of oxygen lack, possibly accentuated by an increased accelerator tone, is to cause an increase in the local production of both auricular and ventricular premature beats.

Increased Systemic Tension.—A rapidly increased systemic tension is associated with an increased vagal and a decreased accelerator tonus. These factors apparently do not affect the muscle receptivity of either auricle or ventricle. It seems possible or even probable that the decrease in the number of spontaneous auricular premature beats, following a sudden increase in the tension, is a direct result of increased vagal tone, and that the equally well-known increase in their number

that follows a rapid fall in blood pressure is due largely to an associated accelerator stimulation. The diminished accelerator tone during increased systolic tension and the possibly diminished vagal tone during and after a rapid falling blood pressure may also be factors to be considered. In any case the effect is upon the speed of local generation or revelation of the ectopic rhythm and not upon the receptivity of the heart muscle. These facts and arguments apply with equal force to paroxysmal tachycardia. Spontaneously occurring ventricular premature beats seem to react in different ways to a sudden rise in tension, sometimes being increased and at other times decreased in number, the first change being that most frequently seen. But the change in either direction is often very obviously related to the change in blood pressure as may be shown by sufficient repetition during the course of an experiment. It is easy to account for the increase as being the result of the tension upon the muscle fibers of the heavier load. The decrease when it occurs is more difficult to explain. In either case, although the cause may be obscure, the fact of the occurrence of a change is sufficiently clear.

Vagal and Sympathetic Stimulation.—Stimulation of the vagus experimentally is generally performed above the level of the inferior cervical ganglion, and it is probable that the simultaneous stimulation of the accelerator fibers in the dog may be a cause of the difficulty of obtaining clear evidence, particularly in the case of the ventricle. On the other hand stimulation of the inferior cardiac nerve generally produces a clear result. Even should a few vagal fibers be included the considerable latent period enables the accelerator effect to be clearly differentiated from it.

Alkalosis.—Although the intravenous injection of both acid and alkali was made in the course of this investigation, the effect of sodium carbonate alone is recorded, for injections of acid into the circulation gave very equivocal results whose interpretation is not clear. The lowering of the threshold to stimulation of the cardiac muscle, caused by the intravenous injection of sodium carbonate, cannot be accounted for by variations in blood pressure, for this in the other experiments made no difference in the level of receptivity; moreover, the effect is clearest in the case of the right auricle. There seems to be no doubt that as the speed of the excitation process and of conduction is shortened by a shift of the P_H of the perfusing fluid towards the alkaline side so is there also a definite increase in muscle excitability.

Adrenalin.—The increase in excitability similarly shown for adrenalin cannot be explained by the rise in blood pressure, for greater rises in control experiments caused no increase in the receptivity of the auricular and of the ventricular muscles.

RESULTS

It would appear that anoxemia, increased systemic blood pressure, and vagus and accelerator stimulation have no effect upon the receptivity of the mammalian auricular muscle to stimuli of constant strength. The same is true also, in the case of the ventricular muscle, of the effect of anoxemia, of accelerator stimulation and possibly also of vagal stimulation. The effect of increased systemic pressure upon the irritability of the latter chamber is to produce a change which is not invariably in the same direction. Alkalosis produces an increased receptivity to constant stimuli in both auricular and ventricular muscles. Adrenalin produces a similar effect, and one, moreover, which is due to two factors, an increase in the rate of stimulus production and, independently of this, an increased excitability or receptivity to stimuli on the part of the heart muscle. In contradistinction to these results seen in the case of stimuli of constant strength, spontaneous premature beats both auricular and ventricular are increased in number by anoxemia and accelerator stimulation. Spontaneous premature beats of the auricle are decreased and those of the ventricle increased by raised systolic pressure, spontaneous auricular premature beats are decreased by vagal stimulation. There is thus a clear contrast between the negative effect of these factors upon ectopic stimuli produced by some external mechanism and their positive effect upon premature beats evoked naturally, though as a result of local changes, by the cardiac tissues themselves. The difference is most clearly seen in the accompanying table of results (Table I) in the case of anoxemia and of accelerator stimulation. There would seem to be three possible explanations of the discrepancy: (1) The electrical method used may have been insufficiently delicate to measure the changes that occurred. (2) The parts of the heart stimulated by the artificial and by the natural mechanism may have varied in receptivity or in their power of being affected by the factors introduced. (3) The change may be due to the fact that the threshold of muscle receptivity may not be changed by the factors, particularly those of anoxemia and accelerator stimulation, but on the other hand that the actual rate of stimulus formation or presentation to the muscle is made more rapid. The results obtained by alkalosis and by adrenalin prove that the method is able to detect slight changes in the receptivity of the muscle. That detected after adrenalin in the case of the right auricle was produced by 5 c.c. of a 1 in 1,000,000 solution, and was well marked after injection of 5 c.c. of a 1 in 500,000 solution. The anatomical work of Woollard[20] proves that all parts of the auricle and ventricle are supplied by sympathetic innervation; moreover, anoxemia in which also clearly differentiated results were obtained is a sufficiently general change. *It is here suggested, there-*

TABLE I

FACTORS INFLUENCING THE APPEARANCE OF PREMATURE BEATS

	STIMULUS OF CONSTANT STRENGTH						LOCALLY PRODUCED AUTOGENIC STIMULUS					
	ANOXEMIA	BLOOD PRESSURE CHANGES	VAGUS	ACCELERATOR	ALKALOSIS	ADRENALIN	ANOXEMIA	RAISED BLOOD PRESSURE	VAGUS	ACCELERATOR	ALKALOSIS	ADRENALIN
Auricular	0	0	0	0	+	+	+	−	−	+	not −	+
Ventricular	0	?	? +	0	+	+	+	+	? +	+	not − ? +	+

0 = no change.
+ = increase } in number.
− = decrease }

fore, that the variations in premature beat frequency occurring in the mammalian heart, apart from gross changes in rate or in the refractory period, are the result of the influence of the factors enumerated in the table upon the speed of manufacture or presentation of the local ectopic stimulus. It is interesting to observe that the action of vagus and accelerator stimulation and of intravenous injection of sodium carbonate upon the speed of formation of impulses at the sinuauricular node is similar in result to their effect upon the number of spontaneously occurring premature beats, both auricular and ventricular. Only alkalosis and adrenalin, of the factors investigated, were seen to affect the muscle receptivity to stimulation. In the light of the results of this investigation and of previous knowledge the effect of these agents upon premature beat frequency is briefly as follows: *Anoxemia* has no effect upon excitability but increases the rate of premature beat formation in both auricle and ventricle, when it is of only moderate degree. *Raised systolic blood pressure* has no effect upon auricular receptivity but has a variable effect upon that of the ventricle. It decreases the number of spontaneously occurring premature auricular beats and increases that of spontaneous ventricular premature beats. *Vagus stimulation* has no effect upon auricular receptivity to stimuli, when these stimuli are single and well-removed from the end of the refractory period, but possibly in some cases increases that of the ventricle. Vagal stimulation diminishes the number of spontaneously occurring auricular premature beats and possibly increases the number of those arising in the ventricle. *Accelerator stimulation* has no effect upon auricular or ventricular receptivity to constant stimuli. It increases the production of spontaneously occurring premature beats in both auricle and ventricle. *Alkalosis* increases the receptivity of both auricle and ventricle. It probably does not decrease the spontaneous generation of auricular premature beats. The increase in the receptivity of auricular and probably of ventricular muscle to stimulation produced by *adrenalin* is a direct one upon the heart muscle, and is independent of any additional action upon the sympathetic nerve endings. This distinction does not appear to have been made by previous workers; Sasaki[18] worked upon the isolated perfused heart as did Langendorff,[17] and no control observations upon the pure accelerator effect seem to have been made.

The Bearing of the Results upon the Theories of Parasystole and Reentry.—Premature beats, in the light of the theory of reentry, might be increased in number by a lengthening or by a shortening of the refractory period,[22] provided a condition was already in being that was delaying the course of the passage of the impulse through certain areas of cardiac muscle. These two different postulates hold in the case of anoxemia on the one hand and of accelerator stimulation on the other. If, however, a lengthening or a shortening of the refrac-

tory period of a sufficient degree to effect this had been produced in the above experiments it seems reasonable to expect as a result some obvious variation in the number of premature beats evoked by the stimuli of constant strength, since the recovery curve varies with the length of the refractory period. Yet when the heart was allowed to manufacture its own ectopic stimuli the changes in their number after anoxemia and accelerator stimulation were very definite.

The results do not seem to fit in so well with the theory of parasystole in the case of those spontaneous premature beats that were investigated. Both accelerator stimulation and anoxemia were shown to increase their number in the case of both auricle and ventricle. The former certainly does not prolong the refractory period[21] and anoxemia may be expected to prolong it. The absence of any increase in the receptivity of both auricular and ventricular muscle, in the presence of these two factors, places the onus, so to speak, of producing an increased number of premature beats upon the rate of local formation or presentation of the ectopic stimulus. The similarity of the effects upon the local premature beat formation of vagus and accelerator stimulation and of alkalosis with their action upon the sinus make it tempting to discard both of these theories, except in certain specific cases, in the absence of more definite evidence, and rather to attribute to widely distributed heart muscle fibers, possibly Purkinje cells, latent properties of the sinuauricular node which as a result of certain agencies become revealed should the local conditions be sufficiently favorable.

SUMMARY

1. Premature beats vary in frequency as a result of a number of causes.

2. This variation is produced in most cases by changes in the rate of formation or presentation of the local stimulus.

3. Alkalosis increases auricular and ventricular receptivity.

4. The action of adrenalin in increasing receptivity of heart muscle is independent of any peripheral stimulation of the accelerator nerve endings.

I wish to express my indebtedness to Dr. Joseph Erlanger for much helpful criticism and many valuable suggestions, and, in addition, for the hospitality of his laboratory.

I would also like to acknowledge the valuable mechanical assistance of Mr. John H. Zimmer.

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CONGENITAL HEART DISEASE

Interventricular Septal Defects with Associated Anomalies in a Series of Three Cases Examined Postmortem, and a Living Patient Fifty-Eight Years Old with Cyanosis and Clubbing of the Fingers*

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INTRODUCTION

THE importance of adding to our knowledge of congenital heart disease and especially the need of help in its clinical understanding, so often obscure, demand the report of all instructive cases. During the past year and a half we have encountered four unusual and important examples, three proved at necropsy and one still alive. The three cases examined postmortem all showed interventricular septal defects with various associated anomalies. These four patients form the basis for the present paper.

LITERATURE

Dr. Maude Abbott, in her recent monograph which appears in the 1927 edition of Osler's *Modern Medicine,* has summarized in the most complete manner and brought up to date our present knowledge of congenital heart disease. Her article is based upon the statistical study of 850 defects with autopsy findings, of which 205 were drawn from the Transactions of the Pathological Society of London and the remainder from other literature and her own personal observations.

She states that while defects elsewhere in the interventricular septum are exceedingly rare, pure defects at the base are commoner than is usually supposed, and, in combination with other defects, they rank as the most frequent cardiac anomaly. Among her 850 cases, a localized basal septal defect occurred in 240 and defects elsewhere than at the base in 15 cases, making a total of 255, or 30 per cent. Of the 240 defects at the base, 54 were classed as the primary lesion, and 186 complicated other anomalies. Of the 54 "primary" defects at the base, 8 were complicated by dextroposition of the aorta, leaving 46 cases of "pure" defect at the base uncomplicated by any anomaly except (in 9 cases) bicuspid or supernumerary or (congenitally) defective aortic or pulmonary valves, and (in 5 cases) congenital tricus-

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pid insufficiency. Of the 186 cases of defect at the base complicating other anomalies, 95 were in cases of pulmonary stenosis or atresia, among which dextroposition of the aorta occurred 62 times. In 36 other cases the defect was associated with transposition of the great trunks, in 14 with persistent truncus arteriosus, and in 9 with communication between the base of the aorta and the pulmonary artery or root of the right ventricle (defect of aortic septum). That is to say, in 154 cases of defect at the base of the interventricular septum complicating other anomalies, this defect was associated with an irregularity of the development of the great trunks or of the septum between these. In the remainder of the 186 cases, the septal defect appeared to be an independent arrest of development.

Tetralogy of Fallot.—Again quoting Abbott, the occurrence in the same heart of a defect at the base of the interventricular septum, pulmonary stenosis, or hypoplasia of the developmental type, and dextroposition of the aorta is the commonest of all combinations in congenital heart disease. Hypertrophy and dilatation of the right ventricle and auricle are constant in this condition, the hypertrophy of the right ventricle constituting the fourth pathological element in the complex. Fallot,[1] in 1888, described this combination which is known in the literature as the "Tetralogy of Fallot." A fairly large number of isolated cases have been reported in the literature from time to time, and in 1924, Raab, Weiss, Lowbeer, and Rihl[2] published a paper containing a complete list of clinical and laboratory findings in cases of this kind which had been confirmed by autopsy. A comprehensive summary of all the confirmed cases has been included in Dr. Abbott's recent monograph, with a detailed case report of a patient of Dr. C. P. Howard's who died at the age of twenty-three years. Dr. Abbott lists 41 cases of this combination which corresponds to one and perhaps two of our cases. She has found that persons with this condition have a relatively short span of life, most of them dying before adult life is reached, usually in the first or early in the second decade. The maximum age in her series was thirty-six years (case reported by Lafitte), but of a large number including cases with and without dextroposition, 28 of the patients died in the first decade and 16 in the second. Another patient in her series, listed under pulmonary stenosis with septal defect in which dextroposition of the aorta is not mentioned, lived to the age of twenty-eight. Howard's[3] patient died at the age of twenty-three years, but the average length of life in 96 cases (both with and without dextroposition) was 10.8 years. In one of our cases the patient lived to be twenty-three. The three cases mentioned above are the only ones which we have been able to find which equal or exceed our case in age.

Coarctation of the Aorta.—Dr. Abbott records 237 cases of coarctation of the aorta, but in only two cases was it associated with an interventricular septal defect, indicating that this is a very unusual combination. The length of life of her two cases is not given.

NEW CASE REPORTS

CASE 1.—H. P., a male college student, aged twenty-three years, was first seen by one of us in September, 1925.

Diagnosis (postmortem): Pulmonic stenosis, interventricular septal defect, and dextroposition of the aorta.

History: He had been a blue baby at birth and a variable amount of cyanosis had persisted, being very mild and almost unnoticable at times, but more marked after exertion or when he was suffering from a respiratory infection. In early infancy a diagnosis was made of congenital heart disease. He was seen by a number of able internists in different parts of the country, each one of whom is said to have urged a quiet life and to have given a bad prognosis. His parents minimized the warnings of the doctors to limit very much the patient's activities, and in order to avoid his being a chronic invalid, encouraged him to lead as active a life as possible. At times he engaged in relatively strenuous exercise, such as tennis and horseback-riding. In spite of this, or possibly because of it, he got along very well until the age of twenty-one, when one day he was seized with a convulsion while at commons in college. He was taken to a hospital where he had several more convulsions, each one lasting about fifteen minutes. After recovering from these attacks, he had no more trouble for a period of about two years, at the end of which time he suffered a syncopal attack while out driving in his automobile. He felt badly and stopped his car at the side of the road where he was found unconscious. An hour later he had a convulsion, and when seen by a physician shortly afterward, was found to be markedly cyanotic, and semicomatose. His blood pressure was 90 mm. systolic and 60 mm. diastolic, and he was having occasional premature beats. He was sent into a hospital where he did fairly well for the first three days, after which time he began having occasional convulsions, which lasted about fifteen minutes each time. The next day, when seen in consultation, the convulsions were lasting longer and the patient was becoming rapidly exhausted. He gave a history at this time of having been subject to easy fatigue and fainting spells. He had been suffering from a rapid, forcible and more or less constant palpitation, but no edema, cough, or hemoptysis.

Physical Examination revealed a fairly well-developed and nourished young man, sleepy, and mentally depressed. The respiration was of a sighing character and he was markedly cyanotic, especially as to cheeks, nose, lips, and ears. The pupils were equal and reacted to light and accommodation. On examining the heart, the apex impulse was found to be maximal in the fifth space 10.5 cm. to the left of the midsternal line and 2 cm. outside the midclavicular line. The left border of dullness was 10 cm. to the left in the fifth space. There was no increase in supracardiac dullness. The sounds were of rather poor quality at the apex. There was a slight blowing systolic murmur heard all over the precordium, loudest at the pulmonic area, but not especially marked. There were no thrills. The pulse was small, but the rhythm was normal. The lungs were clear. The liver was tender, and the lower edge could be felt 5 cm. below the costal margin. There was no edema of the extremities, but distinct cyanosis and marked clubbing of the fingers and toes were present. The temperature was 100° F., pulse rate 90, blood pressure 85 mm. systolic and 70 mm. diastolic. Blood counts showed 10,000 leucocytes and 10,000,000 red blood cells per cubic millimeter.

Course: He was given absolute rest; was carefully digitalized, and put on a liquid diet with frequent small feedings. He gradually weakened, and nine days later his temperature rose to 104°, and he died of a respiratory paralysis following a series of convulsions.

Postmortem Examination.—The heart was obtained postmortem and the pathologist's description follows:

The shape of the heart indicated well-marked enlargement of the right ventricle, the apex being very blunt and made up more by the right ventricle than by the left. The left auricle was smaller than normal and the right auricle was larger, but not markedly so. The aorta was unusually capacious. The pulmonary artery and its branches were much smaller than normal. Both the aorta and the pulmonary artery were smooth. The ductus arteriosus was closed as was also the foramen ovale. The heart weight with the great vessels attached was 464 grams. The walls of both the right and left ventricles measured 13 mm. in thickness and the muscle, macroscopically, was normal in appearance. The valve circumferences were as follows: tricuspid 11 cm., mitral 9 cm., aortic 8 cm., and pulmonary 4 cm.

There was a large interventricular septal defect 2.2 cm. in diameter high in the septum just below the aortic valve. The aorta opened just above the septum more over the right ventricle than over the left; that is, there was a definite dextroposition of the aorta. There were two coronary arteries as usual, but the right coronary artery opened off the aorta well above the anterior valve cusp. The left coronary artery opened behind its cusp as usual. Two centimeters below the pulmonary valve, and separating the right ventricular cavity from a small chamber just below the valve was constriction embracing a narrow opening with a fibrous edge, which opening measured only 3 by 5 mm. in diameter.

In the right ventricle there was one papillary muscle and in addition several columnae carneae holding the chordae tendineae of the valve cusps. A delicate interlacing semitranslucent network was seen in places under the endocardium of the right ventricle and crossing the cavity (undoubtedly part of the atrioventricular conduction system). In the left ventricle were two papillary muscles, as normally, with strands of Purkinje network crossing the cavity. The veins over the pericardium were very prominent and engorged.

There was no evidence of endocarditis, myocarditis, or pericarditis, acute or chronic, and there were no intracardiac antemortem thrombi.

Comment.—This case is very remarkable for the unusual length of life. Although the patient was repeatedly seen by various physicians who always gave a hopeless prognosis from infancy, and in spite of the fact that he carried on a fairly normal amount of activity, with a very limited cardiac reserve and more or less constant cyanosis, he lived for twenty-three years, and nearly completed a college course. The only three cases in the literature with this particular defect which equal or exceed this span of life have been mentioned above.

CASE 2.—T. P., a school girl, fourteen years of age was seen by one of us on March 4, 1927, suffering from severe dyspnea.

Diagnosis (postmortem): Interventricular septal defect and coarctation of the aorta.

History: She had been conscious of her heart "pounding" irregularly and intermittently since childhood. She was not a blue baby at birth, but there had been cyanosis of the lips and dyspnea on exertion for years. For the last three or four years she had had occasional spells of aching of the right eye followed by vomiting.

The eyes had always been somewhat prominent and three years ago a goiter appeared. The family history was negative.

The present illness began six days before examination, with diarrhea and vomiting, preceded by a severe cold and sore throat with fever. She had remained in school for a day or two, but then had to go home because of vomiting and pain in the abdomen. She was taking no medicine except iron. Two days after the onset her heart began to palpitate, and the next day she was seen by a local doctor who found her heart beating very forcefully and irregularly, and who diagnosed thyrotoxic heart.

Physical Examination.—The patient was sitting up in bed breathing stertorously in a rapid and labored manner. The skin was pale, and there was marked cyanosis of the face and hands. The eyes showed some exophthalmos. The left lobe of the thyroid gland was enlarged to the size of an egg. The cervical veins were distended. The heart was enlarged, and the apex impulse was of a heaving character, maximal in the fifth and sixth spaces 10 cm. to the left of the midsternum, 2.5 cm. outside the midclavicular line. There was a question of abnormal widening of the supracardiac dullness. Systolic and diastolic thrills could be felt at the third left interspace. The sounds were of fair quality, P_2 greater than A_2. A loud blowing systolic murmur could be heard all over the precordium, loudest at the third left interspace, and a rough, rather blowing diastolic murmur was present along the left sternal border. There was no friction rub or Broadbent's sign. The rhythm was absolutely irregular at a rate of about 180. The pulse was "thready." The bases of both lungs showed dullness, râles, and diminished breath sounds. The liver was slightly enlarged and tender. The spleen was not felt. Sacral edema was marked, edema of the extremities was slight, and there was a question of ascites. The fingers showed some cyanosis but no clubbing. There were no petechiae in the skin.

Three diagnoses were considered: (1) rheumatic mitral stenosis or adherent pericardium, (2) congenital heart disease with patent ductus arteriosus or pulmonary stenosis, and (3) thyroid heart which seemed unlikely. There was evidence, however, of mechanical pressure from the enlarged thyroid gland and a question of a substernal growth.

Course.—The patient was given 4 c.c. of digalen intravenously which was followed by a reduction of the pulse rate to 140 with almost constant bigeminy. Three grains of digitalis leaf were later given by mouth and a total of 18 grains by the next day.

The following day, March 5, she was admitted to the Massachusetts General Hospital where she grew steadily worse. The cyanosis increased markedly, bubbling râles developed in both lungs, the apex rate rose to 180, the blood pressure was 90 mm. systolic and 65 mm. diastolic. She died at 10:25 that evening.

Postmortem Examination.—A necropsy was performed March 6. The left lobe of the thyroid gland was enlarged to the size of a duck's egg, with the lower pole extending into the thoracic inlet, causing a definite fishmouth constriction of the trachea. The gland had the characteristics of a colloid goiter, but at the lower pole there was a small triangular area which macroscopically gave the appearance of malignancy. On microscopic examination, however, a section through this portion showed small alveoli, containing almost no colloid, with slight hyperplasia of the epithelium.

On opening the pericardium, signs of an early pericarditis were present. The heart weighed 480 grams and was greatly enlarged in all cavities, but especially the right ventricle which was much dilated. The wall of the right ventricle was of extraordinary thickness, measuring 15 mm. The columnae carneae were enormously enlarged, two of them measuring as much as 1.5 cm. in diameter. The left ventricle showed moderate dilatation, and the wall measured 17 mm. in thickness. Its

columnae carneae were hypertrophied but not to the same extent as in the right ventricle. In both ventricles could be seen transverse bands of yellow opaque material (tigering) just beneath the endocardium. Between the two ventricles, close to the pulmonary and aortic valves in the pars membranacea of the interventricular septum was a circular defect 2 cm. in diameter. The valve circumference measurements were: mitral 10 cm., aortic 7 cm., tricuspid 12 cm., and the pulmonary 8 cm. The edge of the posterior cusp of the pulmonary valve was somewhat thickened; otherwise the valve surfaces were negative. The coronary arteries were normal. There was slight dextroposition of the aorta with not more than a quarter of the opening overriding the right ventricle. For a distance of 6 cm. from the aortic valve the aorta measured 6 cm. in circumference, but at the site of the obliterated ductus arteriosus there was a fairly well-marked coarctation which reduced the circumference of the lumen to 3 cm. for a distance of about 1 cm., beyond which it again widened out.

Comment.—This case was one of congenital heart disease with a large ventricular septal defect, a greatly hypertrophied right ventricle, and a slight coarctation of the aorta. There was apparently little cardiac reserve, and a right to left shunt developed on effort. Marked terminal cyanosis was brought on by an acute infection plus mechanical pressure of the thyroid tumor on the trachea. It is a question as to whether there was any thyroid hyperfunction. There was a terminal auricular fibrillation and congestive failure.

CASE 3.—C. R., a boy eleven years old, was seen by us in the House of the Good Samaritan, Boston, in February, 1927. He had been referred from the Boston Children's Hospital and entered the House of the Good Samaritan in September, 1926.

Diagnosis (postmortem): Pulmonary stenosis, absent pulmonary valve cusps, and interventricular septal defect.

History: The family history was negative. He had had measles, whooping cough, chicken pox, mumps, influenza, pneumonia, recurrent tonsillitis, and frequent head colds. He had had no diphtheria, scarlet fever, typhoid fever, rheumatic fever or chorea. He frequently had a cough. There was no history of epistaxis.

He had been a blue baby at birth and all his life he had tired easily on exertion, becoming dyspneic and frequently cyanotic. He was known to have had some sort of heart trouble since the age of two years. When seen at the Children's Hospital several years before, a diagnosis of congenital heart disease had been made. A complicating rheumatic infection was later suspected.

Physical Examination showed a fairly well-developed and nourished white boy with definite Mongolian facies. The lips were very slightly cyanotic, and the teeth were carious and in poor condition. The tonsils were large and cryptic. The heart was somewhat enlarged both to left and right. A systolic thrill and a short diastolic thrill were present all over the precordium and maximal in the third left interspace at the sternal border. There were a loud systolic murmur and a short harsh early diastolic murmur, both loudest in the third left interspace, transmitted moderately well to the apex and but poorly to the right of the sternum. There was no clubbing of the fingers.

Blood Examination: Hemoglobin 90 per cent; red blood cell count, 4,852,000; white blood cell count, 11,200 per cubic millimeter.

X-ray Report: "The film of the chest shows no evidence of an enlarged thymus. There is infiltration in the lung opposite the right border of the heart, and a de-

formity of the cardiac outline which suggests a pleuropericardial adhesion. The hilus shadows are moderately enlarged. The heart dimensions as taken from a seven-foot plate are: right of the median line 4.4 cm., left of the median line 6.5 cm., great vessels 4.2 cm. wide, internal diameter of the chest 19 cm.'' In January, 1927 an electrocardiogram showed sinoauricular tachycardia, rate 136, deep S- and prominent P-waves in all leads, and right axis deviation.

We made the following comment at the time of our physical examination: ''Probably pulmonic stenosis with interventricular septal defect. The diastolic murmur at the pulmonic area is difficult to explain. It may be due to a patent ductus arteriosus, a complicating rheumatic aortic regurgitation, or some other congenital anomaly which cannot be analyzed now.''

Course.—On February 26 the patient complained of pain in the epigastrium and began to vomit. Appendicitis was suspected and a surgical consultant was called. Because of the unusually high temperature, increased respiratory rate and very slight abdominal signs, pneumonia seemed a definite possibility and the surgeon advised waiting until the next day, but at that time general peritonitis was obvious and the patient's condition did not permit surgical interference. During the next few days he became increasingly toxic and died on March 1.

Postmortem Examination.—A necropsy was performed and general peritonitis with a ruptured appendix was found. Following is the description of the pericardium and heart: A thick fibrous adhesion was found joining the right side of the pericardium to the surface of the right pleura. The pericardial cavity contained about 25 c.c. of straw-colored fluid. Its surfaces were everywhere smooth and glistening. There was a small band of adhesion about 1 cm. long and 2 mm. in diameter binding the superior vena cava to the aorta. Elsewhere there were no adhesions in the pericardial cavity.

The heart weighed 275 grams including the great vessels and a certain amount of mediastinal contents (25 to 30 grams). The measurements of the heart in situ were 4.5 cm. to the right of the midsternal line and 5 cm. to the left, both maximal measurements. The greatest longitudinal diameter from the apex to the right auricular appendage was 9 cm.; the greatest transverse diameter was at the auriculoventricular groove, 8 cm. The maximal internal diameter of the chest was 19 cm. The heart gave the impression of being greatly enlarged since its anteroposterior diameter was fully equivalent to its transverse diameter. On superficial inspection the large vessels at the base presented no anomalous arrangement, and the heart itself showed superficially nothing unusual except a marked right-sided hypertrophy involving not only the ventricle, but the auricle as well. The conus arteriosus of the right ventricle was also unusually prominent, and when opened was found to be very much narrowed. The pulmonary ring was only 1 cm. in circumference. The pulmonary valve cusps were entirely absent. The myocardium just below the pulmonary valve was thin, tough, and considerably paler than elsewhere. Immediately above the ''valve ring'' the pulmonary artery was dilated as it entered a large chamber which extended well out into the lungs and had a maximum circumference of 5 cm. From this rose the various pulmonary branches leading to the lungs. The pulmonary veins entered in the usual manner into a small left auricle which connected with the ventricle through a mitral valve presenting nothing of note. The left ventricle was quite small, its cavity being only about one-fourth that of the right ventricle. At the base of the interventricular septum, in the auriculoventricular line was a large defect, semicircular in shape. The base of the semicircle measured fully 1.5 cm. The aortic ring was found to be riding directly over this defect and measured about 4 cm. in circumference. There was no anomaly of the aortic cusps and the aortic valve presented nothing unusual. There was a very small slit-like patent foramen ovale measuring 1 mm. in width and 3 mm. in length. The ductus

arteriosus was not found, and was represented only by a dimple in the aorta. At the point where the aorta was adherent to the superior vena cava, the wall was slightly thickened and there was a slight protrusion of the aortic wall. The myocardium, with the exception of the right conus arteriosus, was quite firm and uniformly dark red. The walls of both the left and right ventricles were 1 cm. in thickness. The valve circumference measurements were: tricuspid 8.5 cm., mitral 7.5 cm., pulmonary 1 cm., and the aortic 4 cm.

Comment.—This case is unique in that the pulmonary valve cusps were entirely wanting. Cases have been reported in which the leaflets were rudimentary, or in which one cusp was missing, but we have been unable to find in the literature any case comparable to this one. In a personal communication from Dr. Maude Abbott, she states that she remembers no congenital heart in which there was a complete absence of the pulmonary cusps.

Another prominent feature was the marked susceptibility to infection suffered by this boy. In addition to the usual children's diseases, he had some sort of respiratory infection a good share of the time, and frequent attacks of tonsillitis. His life was terminated not directly by his heart condition, but by an overwhelming infection. Just what the relation was between the cardiac condition and this low resistance to infection is difficult to say. The very slight degree of cyanosis which was present most of the time would not indicate any marked amount of oxygen unsaturation in the capillary blood, and some other unknown factor must have been responsible.

CASE 4.—H. G., male, married, aged fifty-eight years, a composer of music, was sent to the consultation clinic of the Massachusetts General Hospital March 8, 1927, because of cyanosis and increasing general debility.

Diagnosis.—Probably pulmonary stenosis and interventricular septal defect.

History.—A grandfather and two aunts had died of heart disease. He had a wife and two children living and well. He had had rheumatic fever at the age of ten years, scarlet fever in his youth, and typhoid fever at thirty-two. He had been cyanotic all his life and had always had to limit his activity. His fingers and toes had always been clubbed. Twenty-six years ago he had an embolus which affected his speech, and fifteen years ago another resulting in marked but temporary speech defect. One year ago there was a partial paralysis of the right hand. For years he had been troubled with sparkling scotomata, headache, and visual defects. About six or eight months ago he had an attack of nausea and vomiting at which time his local doctor found albumin in the urine. Three months ago, after catching cold, one foot became swollen and there was a marked increase in a chronic nasal discharge which had been present for many years. Convalescence was very slow. Ten days ago he had an attack of vertigo, dizziness, and vomiting for two days, and since this time he had had some dizziness and slight tinnitus. He felt that he had been "going down hill" for the past year, and he had noticed a marked increase in dyspnea on exertion recently.

Physical Examination showed marked cyanosis, especially of face and hands. Pupils were normal. Teeth false. Lungs clear. The heart was somewhat enlarged, with the left border of dullness in the sixth space 9 cm. to the left of the midsternal line. There was no increase in supracardiac dullness and no thrills were felt. The heart sounds were of poor quality; the first sound was almost replaced over the

entire precordium by a short rough systolic murmur heard loudest in the fourth left space and at the apex. No diastolic murmurs were heard. The second sounds were very faint. The blood pressure was 125 mm. systolic and 95 mm. diastolic. The liver edge was palpable.

The hemoglobin was 80 per cent. A red count was not done. The urine showed a trace of albumin and a few granular casts.

A seven foot plate of the chest showed the transverse measurements of the heart slightly increased and a slight tortuosity of the aorta. There was no marked variation in the shape, but probably slight enlargement of the left ventricle. The measurements were 3.8 cm. to the right of the midsternal line, 9.2 cm. to the left of the midsternal line, total transverse diameter 13 cm., length 13.3 cm., base 11.1 cm., great vessels 5.4 cm. in width, and an internal chest diameter of 25.1 cm.

An electrocardiogram showed normal rhythm, rate 65, diphasic T in all leads, P_2 prominent (4 mm.), and right axis deviation (index −18, angle + 140°).

Comment.—It is our opinion that this patient undoubtedly has congenital heart disease with a venous-arterial shunt. Probably this lesion is a stenosis of the pulmonary artery, possibly low in position as suggested by the site of the maximal murmur with interventricular septal defect. He seems to have an abnormal cerebral circulation.

This patient came to us primarily for the purpose of inquiring about the advisability of making a trip to Europe this summer (1927), to be present at the production of one of his compositions which is to be played at a music festival. The examining physicians agreed that if he did not overtax himself, the trip would probably do him no harm, but excitement and fatigue were to be strictly avoided.* Even though this man is suffering from congenital heart disease and has been more or less of a cardiac cripple all his life, he has not been prevented from becoming a useful member of society or from giving to the world the benefits of his musical talent. He is remarkable not only from the standpoint of his advanced age, but also because of the extent of his accomplishments in spite of the handicap under which he labors.

So far as we can discover, whatever the defect is, this seems to be a record case so far as longevity is concerned. In Dr. Abbott's series there are only three others with cyanosis which approach this age. One reported by Vulpian[4] was a case of pulmonary stenosis, dextroposition of the aorta, and septal defects (not strictly Fallot's tetralogy) in a man who lived to be fifty-two years old. Heddinger[5] reported a case of cor triloculare biatriatum with tricuspid atresia and transposition of the arterial trunks, the patient being fifty-six years of age; and Lallemand[6] published a case of pulmonary stenosis with closed ventricular septum in which the patient had attained the age

*A letter from Germany in July, 1927, reported our patient in fair health and enjoying the music festival. He was seen September, 1927, in better condition than at the time of his original examination.

of fifty-seven. Our patient owes his long life partly to the extremely good care which he has taken of himself and partly to the fact that he has been watched over with great care by a very solicitous wife.*

DISCUSSION

Cyanosis in Congenital Heart Disease.—Lundsgaard and Van Slyke,[7] in 1923, published a paper which discussed cyanosis in detail and contained the results of a large series of studies of the oxygen content of the blood in various normal and disordered conditions of the circulation. Abbott[8] has given an interesting review of their paper with especial attention to its application to congenital cardiac defects. As she has pointed out, this work of Lundsgaard and Van Slyke "dispels much of the confusion surrounding our ideas of this condition (cyanosis) and also throws a searchlight across many obscure questions in cardiac decompensation."

Four possible factors in the production of cyanosis are recognized: decreased pulmonary oxygenation, stasis in the systemic capillaries, increased hemoglobin total, and entrance of venous blood into the arterial stream. The oxygen capacity of the blood is normally about 20 volumes per cent, and in normal individuals the blood emerges from the lungs 95 per cent saturated, which means that the arterial blood contains normally 19 volumes per cent of oxyhemoglobin and 1 volume per cent of oxygen unsaturation. An increase of this unsaturation in the arterial blood coming from the lungs is the first "influencing factor" in the production of cyanosis. In passing through the tissues the blood loses 5 volumes per cent of oxygen, and it therefore emerges in the veins with 14 volumes per cent of oxyhemoglobin and 6 volumes per cent of oxygen unsaturation. It is readily understood that if, through a slowing of the blood stream in the capillaries or by some other cause, oxygen consumption in the tissues be raised above 5 volumes per cent, the "threshold value" of cyanosis will be passed. This is the second possible factor in the production of cyanosis. The third factor is pointed out to be an increase in the total hemoglobin of the blood. An increase in hemoglobin tends to influence the degree of oxygen unsaturation produced by decreased pulmonary oxygenation and acts in conjunction with this factor to deepen cyanosis, but is of relatively little effect alone. Finally, a fourth factor arises in certain pathological states of the circulation, when by passage through a cardiac septal defect in certain congenital lesions, a portion of unaerated venous blood is projected directly into the arterial stream. This is a very powerful factor in producing cyanosis, and when it is combined with stasis in the systemic capillaries as it may be in pul-

*We have recently seen another man, aged fifty-two years, who probably has pulmonary stenosis and septal defect, with a slight but constant cyanosis, who leads a fairly normal life, and although he does not have a great deal of cardiac reserve, he is not severely handicapped.

monary stenosis with septal defect, its effect is very marked. Lundsgaard and Van Slyke have shown experimentally that, other factors being equal, cyanosis does not appear until the amount of venous blood shunted into the arterial stream is equal to one-third of the arterial current into which it flows.

Applying these principles to the cases in the present series, cyanosis in the first case was due to three contributing factors; namely, first and most important, admixture of venous with arterial blood through a septal defect and dextroposition of the aorta; second, capillary stasis due to the pulmonary stenosis, and third, an increased hemoglobin content. Dextroposition of the aorta permits an additional admixture which would not be so great were the aorta in its normal position, for the right ventricle forces venous blood not only through the septal defect into the left ventricle, but a considerable stream is sent directly into the aorta.

In Case 2 the cyanosis was due probably to mixture of venous with arterial blood through the septal defect and some slight dextroposition of the aorta, and to congestive heart failure with capillary stasis and pulmonary edema.

In Case 3 there were undoubtedly two factors responsible for the cyanosis; namely, the pulmonary stenosis resulting in a slowing of the blood stream, and a venous-arterial shunt through the interventricular septal defect and the slightly patent foramen ovale.

Since we have not had the opportunity of examining the heart in Case 4 we shall have to reserve our judgment as to the causative factor here, but it seems likely that a septal defect will explain it, either ventricular or auricular in site.

Physiologically, the pressure in the left ventricle is several times greater than in the right ventricle and so long as this relation is maintained, the shunt in the presence of a septal defect will be of the arteriovenous type which, of course, produces no cyanosis. However, in congenital heart disease where there are pulmonary stenosis and septal defects, the right side of the heart becomes hypertrophied, and it is reasonable to expect that there will be more or less of an equalization of pressure under these pathological conditions. If then, any other factor, such as strenuous exertion, respiratory infection, or any condition which raises intrapulmonary pressure is superimposed, as in the case showing pressure from the thyroid on the trachea, the balance will be thrown the other way, and a venous-arterial shunt will result with its concomitant cyanosis.

The Clinical Diagnosis of Interventricular Septal Defects and Associated Anomalies.—A pure septal defect without pulmonary stenosis or dextroposition of the aorta rarely produces cyanosis except as a terminal event. Subjects may pass through life with no symptoms whatsoever. The most important sign in the majority of such cases is

a prolonged and constant systolic murmur (Roger's murmur) usually heard best at the third and fourth left interspaces near the sternum and transmitted with diminishing intensity in all directions; it is heard usually in the back, but not in the vessels of the neck. The harshness and intensity vary inversely as the size of the defect. There is a purring systolic thrill, according to Dr. Abbott, in about one-third of the cases. When this condition is complicated by dextroposition of the aorta there is practically always cyanosis of moderate or marked degree and there may or may not be clubbing of the fingers. In case of a large septal defect with dextroposition, the thrill may be absent and the murmur slight due to the fact that the blood may pass with ease into the aorta. If, in addition, there is a complicating pulmonary stenosis, the cyanosis is apt to be more intense, the murmur more pronounced, and a thrill, localized at the second and third left interspaces or diffuse over the entire precordium, is said to be fairly frequent. With pulmonic stenosis the pulmonary second sound is weak or absent in a certain proportion of patients, but in a limited number of Dr. Abbott's cases it was distinctly louder than normal. A prolonged harsh rasping or blowing systolic murmur heard over the whole precordium, but chiefly at the base, with its point of maximal intensity to the left of, or over the upper part of the sternum and the second interspace, is present in the great majority of cases. It is transmitted upward along the clavicle, along the course of the pulmonary artery and over the sternum, but is faint or inaudible at the apex and to the right of the sternum.

Our four cases showed cyanosis of varying degrees. The fingers were clubbed in two of them; these two had no thrills. In Case 3 with pulmonary stenosis and regurgitation, interventricular septal defect and dextroposition of the aorta, there was a systolic thrill maximal at the third left space near the sternum and both systolic and diastolic murmurs were heard at the same point. In Case 2, with interventricular septal defect, dextroposition and coaretation, there were systolic and diastolic thrills and murmurs in the third left interspace. In Case 1, with interventricular septal defect, dextroposition of the aorta and infundibular stenosis, there were no thrills and only a slight systolic murmur to the left of the midsternum.

The electrocardiogram is oftentimes very helpful in the diagnosis of congenital heart disease as it has certain fairly constant characteristics. The P-wave is usually prominent and the QRS complex in some cases is apt to be bizarre. With pulmonic stenosis and most septal defects, the right side of the heart becomes markedly hypertrophied and this manifests itself as a right axis deviation. We obtained electrocardiograms in two of the cases here reported and they both conformed to this general rule. The record in these conditions may resemble very strongly that of mitral stenosis, but the history

and physical signs are ordinarily distinctive enough to differentiate between the two.

The most characteristic x-ray features are the relatively small size of the left ventricle and the great hypertrophy of the right ventricle. There is prominence of the second left, or pulmonary, arc which is enlarged and pulsating in most cases of long standing, and which has been ascribed, by the French writers especially, to a dilatation of the pulmonary artery above the point of stenosis. Such a dilatation, however, is by no means constant, for on the contrary, there is an associated hypoplasia of the pulmonary artery in most cases of stenosis of the developmental type, so that some other causes for the second left arc must be found. Usumoto[9] investigated 10 such cases, in two of which autopsy showed that the large second arc of the radiogram on the left side was due not to a dilated pulmonary artery but to a greatly hypertrophied conus of the right ventricle. Although the electrocardiogram and x-ray picture are interesting and often helpful, the diagnosis in these conditions rests mainly on the presence or absence of cyanosis, clubbing, and thrills and murmurs localized over the pulmonic area and just below.

The Prognosis in Interventricular Septal Defects and Associated Anomalies.—The prognosis in congenital heart disease is extremely variable and is affected by a number of factors. According to Dr. Abbott, it depends largely on the effects of the lesion upon the circulation, that is, upon the amount of cardiac strain or the degree of oxygen unsaturation induced by the defect, and upon the compensatory powers. For this reason, symptoms will frequently prove a better guide to the immediate future than physical signs. A septal defect may give a marked murmur and thrill, yet lead to no hampering of the heart's action and to little interference with oxygenation until some additional factor, such as obstruction in the pulmonary circulation supervenes, producing a transient or terminal cyanosis. Persistent cyanosis, a continued low temperature, a marked increase in the red cell count (above 5,500,000), and a dilatation of the heart all point to a grave disturbance of the circulation and often lead to a rapidly fatal issue.

On the other hand, the entire absence of cyanosis and its attendant phenomena does not always mean a favorable prognosis, for in such cases sudden death may occur without warning, either quietly or in a paroxysm of cyanosis with dyspnea. The embarrassment to the circulation which the lesion itself entails is not the only source of danger. Grave peril lies also in the intercurrence of a bacterial endocarditis in those patients who attain early adult life, and in the fact that infections, such as bronchopneumonia, are apt to prove rapidly fatal. The liability of patients with pulmonary stenosis to tuberculosis, and the occasional termination by sudden cerebral complications

are other unfavorable factors. Clubbing of the fingers in itself is probably of little significance.

Among people of the better class, where good hygiene prevails and the most suitable conditions of living are available, the outlook is much brighter than among the children of the very poor.

SUMMARY AND CONCLUSIONS

Four cases of congenital heart disease with interventricular septal defects and various associated anomalies have been here presented. Two of the cases are apparently unique. All had some degree of cyanosis, and two had clubbing of the fingers. Three came to autopsy and the fourth is still living at the age of fifty-eight years. Case 1 was a man twenty-three years of age with the tetralogy of Fallot: pulmonary stenosis, interventricular septal defect, dextroposition of the aorta, and large right ventricle. Case 2 was a girl fourteen years old with interventricular septal defect, moderate coarctation of the aorta, and slight aortic dextroposition. Case 3 was a boy of eleven years, with septal defect, pulmonary stenosis, absent pulmonary cusps, and slight dextroposition of the aorta, showing also other congenital stigmas. Case 4 is a man still living at fifty-eight years, showing considerable cyanosis, and clubbing of the fingers and toes, with a probable diagnosis of pulmonary stenosis and septal defect. The first two cases are very unusual, the last two are apparently unique; Case 3 because of the complete absence of pulmonary valves and Case 4 because of his advanced age in the presence of pronounced cyanosis and well-marked clubbing of the fingers.

In the discussion of the mechanism of the production of cyanosis, four factors have been considered: (1) decreased pulmonary oxygenation, (2) stasis in the systemic capillaries, (3) increased hemoglobin total, and (4) entrance of venous blood into the arterial stream.

The diagnosis of congenital cardiac defects rests mainly on the presence or absence of cyanosis, clubbing, and the thrills and murmurs localized in and around the pulmonic area, with considerable aid often from the electrocardiogram and radiogram.

Prognosis is very difficult in these cases. It depends largely upon the degree of cardiac involvement, the amount of cardiac reserve, the ability to resist infections, and the economic conditions to which the patient must adapt himself.

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AN EXPERIMENT IN VOCATIONAL TRAINING CARRIED ON IN CARDIAC CLASSES OF THE MANHATTAN TRADE SCHOOL FOR GIRLS*

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HISTORY OF THE CARDIAC TRADE CLASSES

THE trade classes for cardiac girls were opened by the Board of Education at 136 East 127th Street on January 1, 1923, as an annex of the Manhattan Trade School for Girls, to provide vocational training in selected occupations for girls with heart disease. The need for classes of this kind was brought to the attention of the Board of Education by the New York Heart Association because the city schools had made no special provision for cardiac children between the ages of fourteen and sixteen who wanted trade training, and also because it seemed advisable to have segregated classes for cardiacs during a period of experimentation.

Since August 1, 1924, the Cardiac Vocational Guidance Committee of the Public Education Association, in conjunction with the Board of Education, has assumed responsibility for developing the trade classes. This Committee, from its staff, assigns to the classes a vocational counselor and a trained nurse who give intensive supervision to both the vocational and the medical problems of the pupils. The Committee has been fortunate in securing the volunteer services of a heart specialist, who examines all applicants for admission, and makes frequent subsequent examinations of the pupils.

The classes are in no sense therapeutic, but are trade classes established for the purpose of training girls to meet the demands of industry, in occupations which do not require a maximum of physical exertion. After studying the industrial field, courses in dressmaking and millinery were chosen as being best suited to this group. The time required for the completion of either course is two years.

The pupils are recruited from four main sources: the cardiac classes of the elementary schools, the suspense register of the Board of Education, the working-paper rejection group of the Board of Health, and the cardiac clinics of the hospitals. The suspense register is kept by the Bureau of Attendance of the Board of Education and concerns those children who are excused from school for a stated time on the order of a physician. The working-paper rejection group consists of those children who have been refused working papers by the Board

*From The Cardiac Vocational Guidance Committee of the New York Tuberculosis and Health Association, formerly a Committee of the Public Education Association. Records obtained by Gertrude Graydon (deceased). Statistical work and charts by Mary B. Herring.

of Health because of a cardiac condition. The examining physician of the classes aims to restrict the group to those children who probably will be able to carry on in industry. Children admitted must also meet the educational requirements for working papers. Since September, 1925, the law has required that every child under seventeen years of age must procure working papers before going to work. To obtain an employment certificate a child must be either fifteen years old and through the 6B grade, or fourteen years old and an 8B graduate. It is the aim of the trade classes to raise the educational standard by admitting only children who have graduated from the 8B grade.

The children remain under careful medical supervision, with special attention given to diseased tonsils, carious teeth, and personal hygiene; but such special daily routine as pulse and temperature taking and daily rest periods is dispensed with, and to a great extent a normal routine is followed. Each day the teacher in charge submits a list of the absentees to the nurse, whose duty it is to find out the reason for each absence. Inquiry is first made of the clinic which the child attends to ascertain whether the social service department has any knowledge of the child's illness. If no information can be gained from this source, a home visit is made by the nurse, whose duty it is also to see that each pupil attends clinic whenever required; for which she gives the child an excuse from school. Recommendations made by the examining physician are carried out under the supervision of the nurse.

The vocational counselor holds an initial conference with each candidate for admission to find out whether the child meets the requirements of the classes, and to help her decide which course to take. Frequent subsequent interviews are held with each child and her teachers, concerning the progress of the child's work. Home and clinic visits are made to secure cooperation with the parents and to keep in touch with the child's physical condition. It is also the duty of the counselor to acquaint school principals, teachers, doctors, nurses, and social workers with the aim and purpose of the trade classes.

In February, 1924, the Board of Education organized at the same location similar classes for boys as an annex of the Murray Hill Vocational School. These classes are carried on with the same requirements, policies, and intensive supervision as are the girls' classes. Courses are offered in mechanical and architectural drawing, jewelry-case making, and leather tooling.

REPORT

The following study concerns 115 girls who were discharged during the first two and one-half years of the trade classes, from February

1, 1923, to June 30, 1925. Because the period was short and the number small, the data are presented with a full realization that no final conclusions can be drawn from them. The report may possibly be suggestive to those communities interested in making a similar study, and the preparation of it has helped to evaluate the work of this experiment.

The purpose of the investigation was to find out, if possible, to what extent the training and the medical supervision offered by the trade classes are valuable to children with heart disease in their subsequent industrial life.

A careful study was made of the school records, medical charts, and case histories of these 115 pupils. A letter was sent to each girl asking her to call at the office. This interview was held in the evening so that it was not necessary for the girl to remain away from work.

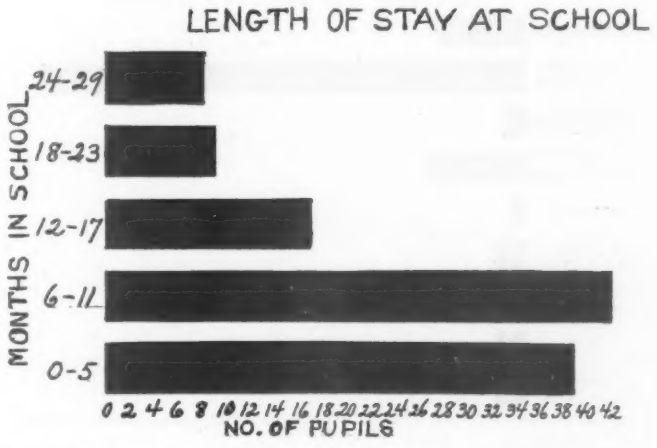

Fig. 1.—Showing the length of time spent in the trade classes.

During the interview, a record was taken of her work, her clinic attendance, and her physical condition since leaving the trade classes. If the girl did not come to the office, the investigator made a home visit. In this way, records of 89 girls were obtained. The cardiac clinics were visited to obtain a medical report of all cases under their supervision.

Fig. 1 shows that 39 girls left the classes during the first six months and that 42 left during the second six months. This means that 81 of the 115, or 70.4 per cent, left before the end of their first year. A large number of these were girls who left to go to work as soon as they became sixteen. At the time of this investigation, working papers were not required of children over sixteen years of age. On September 1, 1925, the age was raised to seventeen. Only 17 of the 115 girls remained eighteen months or more.

In tabulating the reasons for leaving the classes (Fig. 2) it was found that 11 girls completed the course; 68 left to go to work,—65

of these being over sixteen—and 3 passing the Board of Health examination and obtaining working papers before reaching their sixteenth birthday; 13 were transferred to other schools; 2 were married; 4 were needed at home; 9 were too ill to continue in school; 4 died; and 4 moved out of the city. A large number of the 65 who left to go to work gave economic pressure at home as the reason, although it is doubtful whether that was the real reason. Probably the majority left because of the indifference of the parents, or because the girls themselves were eager to work as soon as possible.

The above figures are not unusual for secondary school children. In a study of 455 continuation school children, made in 1924 by the Bureau of Women in Industry of New York City, it was found that 60 per cent of the children left because of economic pressure at home,

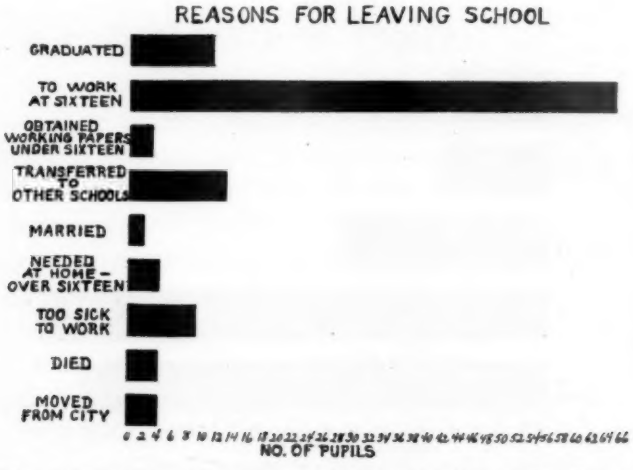

Fig. 2.—Showing the reasons for leaving the trade classes.

and 20 per cent because of dissatisfaction with the school. Studies made in other cities show similar results. In a report of surveys made in a number of cities by the Children's Bureau of the United States Department of Labor, it is stated that from one-third to two-fifths of the children in each city leave school to go to work because of economic necessity.

Earnest efforts were made to keep the children in the trade classes. Frequent consultations were held with the teachers and the parents, and each girl was interviewed by the vocational counselor before she left. A number of scholarships were granted to children in families where there was financial need, but the small sums available were often insufficient to meet the deficit. Every available means was used to bring to the parents a realization of the importance of trade training for children handicapped by heart disease, and to help them understand that such work as running errands, packing, and doing heavy factory work, is unsuitable for these children. It is interesting

to note in this connection that many of the girls who left school to take unskilled positions, in later interviews expressed their regret at not having made an effort to complete their courses. Three were re-admitted to school at their own request, after discouraging experiences at work.

In order to ascertain, if possible, what bearing certain factors had on the large turnover, an analysis was made of the age, the school grade, the intelligence quotient, and the functional classification on admission.

Table I shows that 70 girls, or 60.9 per cent of the total number, entered in their sixteenth year. It is significant that only 4 of these remained to complete the course. Fifteen of the 19 who were over sixteen on admission, left before the end of the first year.

TABLE I

AGE ON ADMISSION CLASSIFIED BY LENGTH OF TIME IN TRADE CLASSES

AGE ON ADMISSION	TOTAL CASES	MONTHS AT TRADE CLASSES				
		0-5	6-11	12-17	18-23	24-29
17	1		1			
16	18	9	5	3		1
15	70	25	28	9	4	4
14	21	4	5	5	4	3
13	5	1	3		1	
Totals	115	39	42	17	9	8

TABLE II

GRADE ON ADMISSION CLASSIFIED BY LENGTH OF TIME IN TRADE CLASSES

GRADE ON ADMISSION	TOTAL CASES	MONTHS SPENT IN TRADE CLASSES				
		0-5	6-11	12-17	18-23	24-29
H. S.-2 yr.	2	2				
H. S.-1 yr.	3	1	2			
8B	41	15	11	7	4	4
8A	3	1	1		1	
7B	11	5	2	2	1	1
7A	37	13	15	6		3
Below 7A	18	2	11	2	3	
Totals	115	39	42	17	9	8

None of the girls with previous high school training completed the course (Table II). It was found that they were not interested in a trade and obtained office positions as soon as they became old enough to work. At the other end of the scale, 13, or 72.2 per cent of the 18 girls who were admitted below the 7A Grade, were over fifteen on entry. Ten of the 13 left during the first year, 8 of whom went to work as soon as they became sixteen. Only one stayed to complete the course.

The intelligence ratings were found to be similar to those of children without heart disease. The majority of those in the high average group and those in the dull normal left before finishing the course:

the former, to take office positions; the latter, because of failure in their work.

The Heart Committee of the New York Tuberculosis and Health Association classifies patients with heart disease as follows:

I. Patients with organic heart disease, able to carry on ordinary physical activity without discomfort.

II. Patients with organic heart disease, unable to carry on ordinary physical activity without discomfort.

A. Activity slightly limited.

B. Activity greatly limited.

III. Patients with organic heart disease, who have symptoms or signs of heart failure when at rest and who are unable to carry on any physical activity without discomfort.

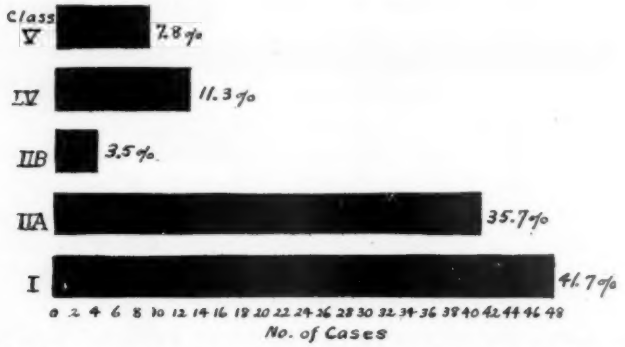

Fig. 3.—Showing the number and per cent of girls in each functional classification at entry.

IV. Patients with abnormal signs or symptoms not believed to be due to organic heart disease.

V. Patients without circulatory disease whom it is advisable to follow because of the presence or history of an etiological factor which might cause heart disease.

Over three-fourths of the girls, or 77.4 per cent, were in either Class I or Class IIA on admission. A study of the original data shows that the average length of time these girls stayed in the trade classes was ten months, the range being from nine days to two years four months.

No correlation is indicated between the functional classification on admission and the length of time spent at school. During the first year 68.8 per cent (Table III) of those in Class I left; 73.2 per cent of Class IIA; 25 per cent of Class IIB; 77 per cent of Class IV; 77.8 per cent of Class V.

Fig. 4 shows the relative functional classifications of 115 girls on admission to the classes; on discharge; and at a subsequent investiga-

TABLE III

IN TRADE CLASSES
FUNCTIONAL CLASSIFICATION ON ADMISSION CLASSIFIED BY LENGTH OF TIME SPENT

FUNCTIONAL CLASSIFICATION ON ADMISSION	TOTAL CASES		MONTHS SPENT IN TRADE CLASSES					
			0-11		12-23		24 and over	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
I	48	100	33	68.8	10	20.8	5	10.4
IIA	41	100	30	73.2	10	24.4	1	2.4
IIB	4	100	1	25.	2	50.	1	25.
IV	13	100	10	77.	3	23.	0	0.
V	9	100	7	77.8	1	11.1	1	11.1
Totals	115	100	81	70.4	26	22.6	8	7.

tion. The majority of the girls remained in the same functional classification during their stay in the classes as on admission. Exclusive of the 4 girls who died while members of the school, 97, or 87.4 per cent, remained in the same classification; 6, or 5.4 per cent, improved; 8, or 7.2 per cent, deteriorated. Of the 4 girls entered as Class IIB, 1 improved and was reclassified as Class I; 1 left to go to work; 1 became too ill to attend school, and 1 died while a member of the school. Of the 41 whose records were obtained at a subsequent investigation, 3 had died. Of the remaining 38, 23, or 60.5 per cent, had remained in the same classification as at the time of discharge; 5, or 13.2 per cent, had improved; and 10, or 26.3 per cent, had deteriorated. In the 41 patients for whom subsequent reports were obtained, there was shown a tendency to change in functional classification more rapidly after leaving the classes than while in attendance. Of these 41, 82.9 per cent remained in the same classification during their stay at school, as compared with 60.5 per cent after leaving; 4.9 per cent improved while at school, as compared with 13.2 per cent after leaving; 12.2 per cent deteriorated, as compared with 26.3 per cent after leaving. Since the number is small, it is impossible to say whether work in school or work in industry affects the heart condition to the greater degree. The results of the subsequent investigation were dependent on clinic attendance, and since, as a rule, children who carry on well and who feel no cardiac symptoms, stay away from clinic, the 41 may not be representative of the entire group.

Figs. 5 and 6 tell a story about the same children, based on a time grouping.

Fig. 5 shows that change in classification increases with the length of stay in school.

In Group *A* only 2.6 per cent of change is indicated; in Group *B*, exclusive of the 2 who died during this period, 10 per cent of change is shown; in Group *C*, exclusive of the 2 who died in this period, 26.7 per cent; in Group *D*, 22.2 per cent; and in Group *E*, 37.5 per cent. Of the 39 who left during the first six months, 38 remained in the

same classification as on admission, and 1 improved; of the 42 who left during the second six months, 36 remained in the same functional classification, 2 improved, 2 deteriorated, and 2 died; of the 17 who left during the third six months, 11 remained in the same class, 1 improved, 3 deteriorated, and 2 died; of the 9 who left during the fourth six months, 7 remained in the same class and 2 deteriorated; and of the 8 who left during the last period, 5 remained in the same class, 2 improved, and 1 deteriorated.

Fig. 6 shows that of the 12 for whom clinic reports were obtained during the first six months after discharge, 7 remained in the same functional classification, 3 improved, and 2 deteriorated (41.7 per cent change); of 13 who had clinic reports during the second six months after discharge, 6 remained in the same classification, 1 improved,

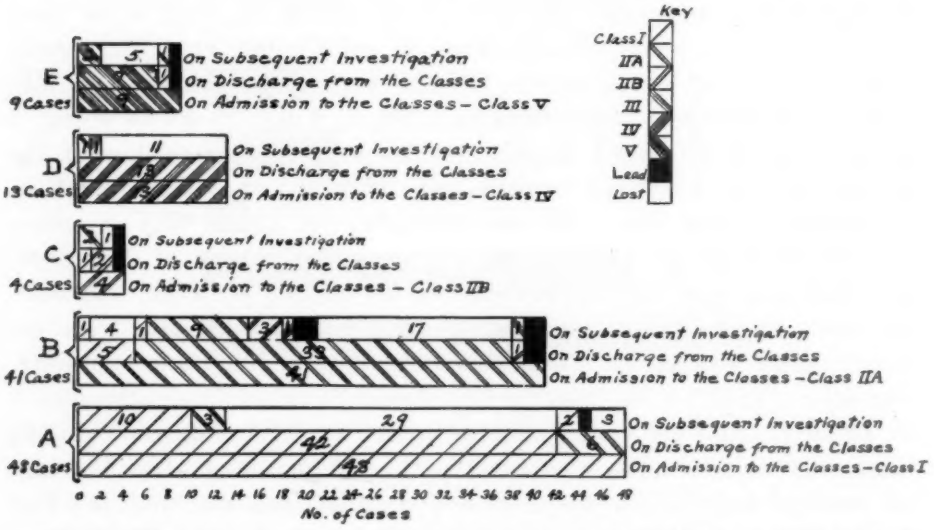

Fig. 4.—Five groups of curves are shown, each group consisting of three horizontally arranged columns. In each group the lowest column represents by its length the number of cases in the group, and by its lines the functional classification on admission; the middle column represents the fate of the same children on discharge from the classes; and the top column represents the fate of the same children at an investigation subsequent to their discharge. Group *A* concerns the 48 children who were in Class I on admission; Group *B*, the 41 children who were in Class IIA on admission; Group *C*, the 4 children who were in Class IIB on admission; Group *D*, the 13 children who were in Class IV on admission; and Group *E*, the 9 children who were in Class V on admission.

and 6 deteriorated (53.9 per cent of change); of the 8 for whom clinic reports were obtained during the third six months after discharge, exclusive of the 2 who died during this period, 5 remained in the same classification and 1 deteriorated (16.7 per cent of change); of the 6 for whom reports were received during the fourth six months after discharge, exclusive of the 1 who died, 4 remained in the same classification and 1 improved (20 per cent of change); and of the 2 for whom reports were obtained during the fifth period, 1 remained in the same classification and 1 deteriorated (50 per cent of change).

The correlation of increase in change of classification with the

length of stay at school which is shown in Fig. 5 (115 cases) does not hold for the 41 cases whose records were considered over similar periods of the time, after leaving school.

Table IV shows the causes of death of the 7 who died; the last diagnosis and classification at the trade classes; the time between the

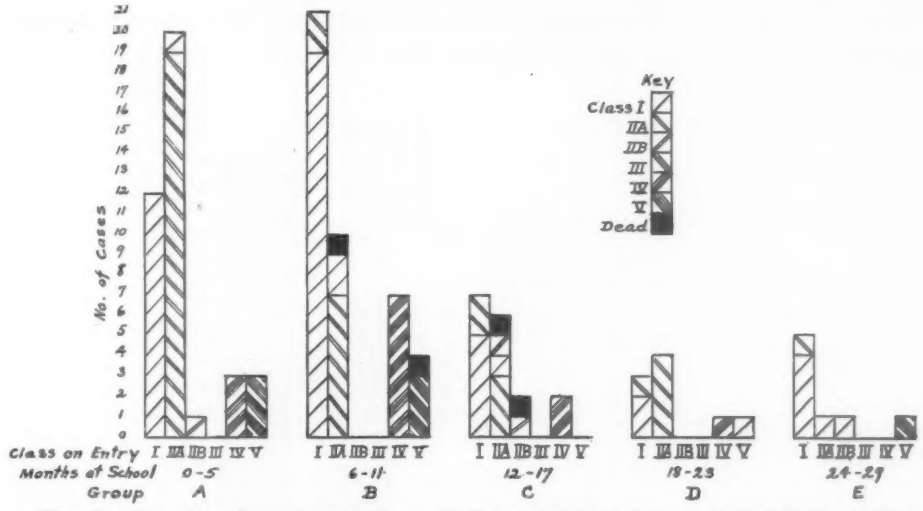

Fig. 5.—Showing five groups of vertically-arranged columns illustrating changes in functional classification during a six-month period based upon the length of time the children remained in school. In Group *A* are those who were members of the school less than six months; in Group *B* those from six to twelve months; in Group *C* those from twelve to eighteen months; in Group *D* those from eighteen to twenty-four months; in Group *E* twenty-four months or more. Underneath each column is the classification on admission; the height of the column shows the number who entered in that class; and the grouping within the column indicates the classification on leaving.

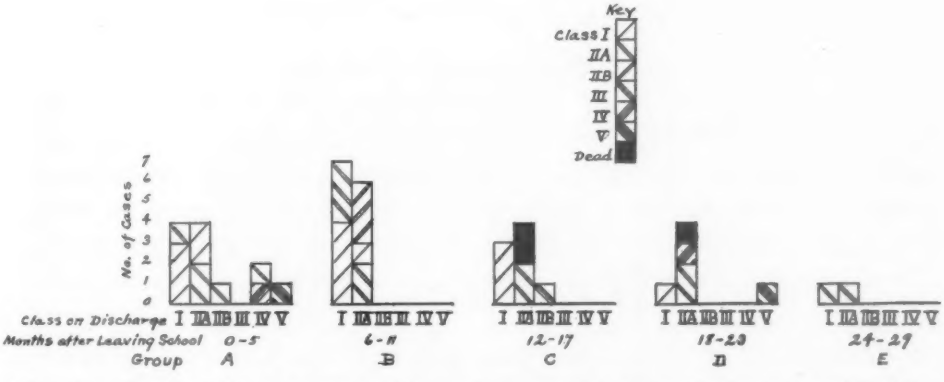

Fig. 6.—Showing the changes which were uncovered on subsequent investigation. The data were obtained from the clinics.

last classification and the date of death; the kind of work and the length of time at work of those who died after leaving school.

As stated before in this report 89 girls were interviewed after leaving school. Of these, only 50 were receiving medical care at the time they were investigated (Fig. 7). Thirty-seven were attending cardiac clinics and 13 were under the care of private physicians. Of those in

TABLE IV

CAUSE OF DEATH	LAST DIAGNOSIS AT SCHOOL	LAST CLASSIFICATION AT SCHOOL	TIME BETWEEN LAST CLASSIFICATION AND DATE OF DEATH	LAST OCCUPATION	KIND OF WORK	LENGTH OF TIME AT WORK
Heart failure	M.I.-M.S.	IIB	3 months	Member of school		
Heart failure	M.I.-A.I. Auricular fibrillation	IIB	16 months	Member of school		
Heart failure (sudden after strain)	M.S.	IIA	6 months	Member of school		
Appendicitis	Chorea	V	7 months	Member of school		
Pneumonia	M.I.-M.S.	IIA	15 months	In industry	Unskilled—factory	4 months
Pneumonia and complicated heart disease	M.I.-M.S.	IIA	20 months	In industry	Millinery—factory	17 months
Heart failure	M.S.	IIA	17 months	In industry	Unskilled—factory	14 months

Class I, 17 were attending clinic, 7 had a private physician, 15 were having no treatment, and for 2 no report was obtained; of those in Class IIA, 15 were attending clinic, 2 had a private doctor, 12 were receiving no treatment, and for 1 no report was obtained; of those in Class IIB, 2 were attending clinic and 1 was under the care of a private physician; of those in Class IV, 2 were attending clinic, 3 were under the care of a private physician, and 4 were receiving no treatment; of those in Class V, 1 was attending clinic and 5 were receiving no treatment.

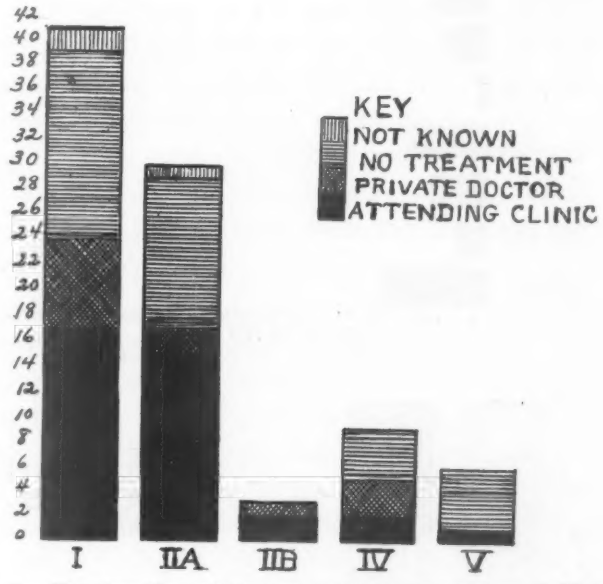

Fig. 7.—Showing the subsequent medical supervision of 89 girls.

Of the 61 girls who were working at the time of the investigation, about three-fifths were attending clinic. There is a tendency among this group to drop out of clinic after leaving school. A number of hospitals do not have evening clinics and the girls cannot be spared from work during the day. In many cases, especially those in Class I, where they are not conscious of cardiac symptoms, they neglect to avail themselves of medical supervision, and fail to keep their appointments.

Fig. 8 is a follow-up record of the entire group of 115 girls at the time of investigation. Sixty-one were working, 7 were attending other schools, 7 were staying at home, 5 had married, 1 had been pronounced noncardiac, 10 were too ill to work, 7 had died, 4 had moved away, and 13 could not be located.

The relation of the training at the trade classes to later work is shown in Fig. 9. Thirty-one, or slightly more than half of the working group, were employed at the trade they learned in the classes, or at related trades. Thirty were in nonrelated trades. Those who

learned dressmaking were found in trades closely related to dressmaking. Among these are included machine-operating and crochet-beading on dresses, finishing on negligees, hand sewing on dress trimmings, and examining underwear. In the trades designated as "unrelated" are included unskilled factory work, such as labelling,

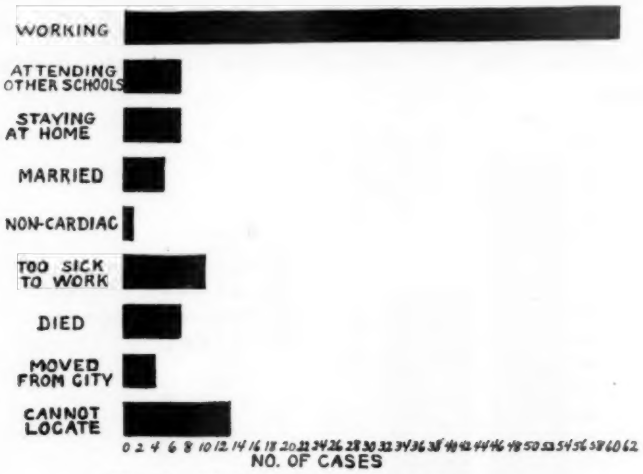

Fig. 8.—Follow-up report of 115 cases.

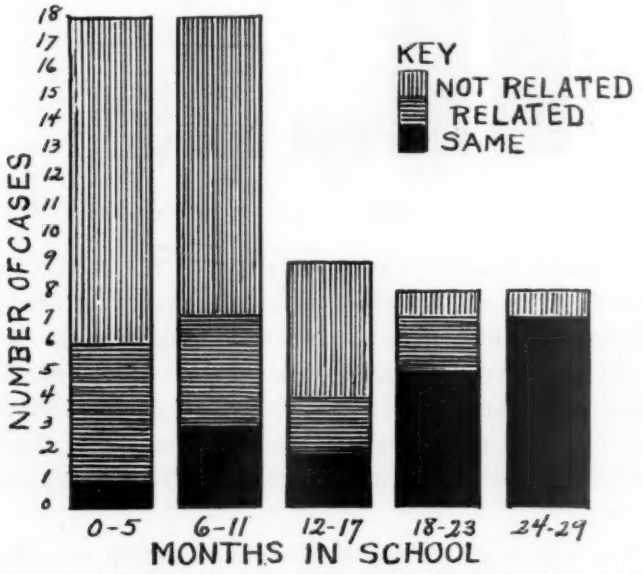

Fig. 9.—Showing the relation of type of work to trade training in the classes—61 cases.

assembling, packing; unskilled labor in department stores, other mercantile establishments, and wholesale houses, such as stock clerk, floor girl, messenger, etc.; and clerical positions.

How great an advantage it is to these children to have learned a trade can be shown from the point of view both of health and of economics. The trades in general supply the opportunity for earning

a better wage and for engaging in work much less arduous than found in the field of unskilled labor.

In the sewing trades, trained workers usually receive the same beginning wages as do untrained workers, but are placed in types of work that assure much more rapid advancement. Trained workers are not required to run errands or do other work which would retard their progress and be undesirable for girls with heart disease. Those who had completed the course at the trade classes were placed at beginning wages of from $12 to $15 a week. Four months later two dressmakers reported raises to $17 and $18 respectively; one milliner was advanced from $12 to $15 at the end of three months. Many who left during the early months to take unskilled positions in factories or stores had not had a raise in wages for a year or more. At the time when they were interviewed all who had completed the course were still in the positions in which they were first placed, while those who were doing unskilled factory work had held more positions with longer periods of unemployment than those engaged in dressmaking, millinery, or related trades. This corresponds with the results of studies made of physically normal workers.

Forty of the 61 in the working group had lost no time from work on account of illness. During periods ranging from one month to two years at work, 7 had been absent less than one week, and 9 had been absent more. Three reported rheumatism as the cause of absence; four, a heart condition; and nine, other illnesses. Ten girls were too ill to work. Eight had left the classes for this reason, and the other two had broken down after working for a short time.

SUMMARY

1. The children at the trade classes are handicapped by the fact that many of them do not remain there long enough to learn their trade. The chief reasons for leaving are financial pressure at home and the lack of realization on the part of both parents and children of the importance of learning a trade. This is a problem common to most secondary schools.

2. The majority of the girls who completed the course and who remained a year or more, were working at the same or related trades at the time of investigation.

3. The findings seem to indicate that the children with considerable training who entered related trades were earning higher wages and had remained in the same jobs longer, with shorter periods of unemployment, than those who entered occupations not related to their trade training.

4. It is difficult to obtain reports of the subsequent health history of these children, as many of them—especially those who feel no heart symptoms—do not attend clinic after going to work. The percentage of changes in functional classification of those whose records were obtained was greater after going to work than while attending the trade classes.

5. Those falling in the classifications of I and IIA carried on while in school as favorably as normal children. Those in IIB were absent more and could not carry on the normal work without frequent rest periods and constant supervision.

6. The majority of the girls at work were able to carry on without losing time on account of ill health.

RECOMMENDATIONS

1. Children should be selected for the trade classes who in all probability will complete the course. The following groups ought to be excluded:

   A. Children who are of too low grade mentally to learn a skilled or semiskilled trade.

   B. Children who are classified by the admitting physician as Class IIB, III, IV, or V.

2. Parents of cardiac children and the children themselves should be educated to the importance of such training as will enable these children to enter the skilled or semiskilled occupations.

3. The children should be made to understand the importance of attending clinic after they go to work. The doctors and the social workers of the clinics should assist the vocational counselor in attempting to accomplish this.

4. Since the findings, pertaining to the children other than IIB's, are similar to those of noncardiac children, it does not seem necessary to continue segregation for cardiacs if adequate medical supervision can be given such children in the regular trade schools.

Department of Clinical Reports

POSTURAL HYPOTENSION*

An Autopsy Upon a Case

Samuel Bradbury, M.D., and Cary Eggleston, M.D.
New York, N. Y.

IN OCTOBER, 1925, we reported† the clinical and pharmacological investigation of three patients who exhibited remarkable changes of blood pressures in response to changes of posture. Each patient complained of syncopal attacks after exertion or even upon standing erect for a few minutes; other features of their condition were: incapacity to perspire, a slow unchanging pulse rate, lowered basal metabolism, and slight and indefinite changes in the nervous system. The systolic blood pressures of these patients would drop precipitately 50 per cent or more upon changing from the supine to the erect posture, the diastolic fall being proportionate to the systolic.

As reported in our paper one patient died suddenly in June, 1925; the others then being alive and with no changes in their condition. Now, the third patient is still alive and in the same condition; but a second patient (L. H.) died at City Hospital September 25, 1926.

He had appeared to be in his usual condition until 4 P.M. that day; then on his way to the bathroom he fainted; this time, however, he did not recover consciousness but became worse and was pronounced dead in ten minutes.

A postmortem examination was made upon this patient September 28. Unfortunately it was incomplete, as examination of the brain was not permitted. The hypothesis upon which we attempted to explain the disorders in these three patients was paralysis of the sympathetic vasoconstrictor endings, and had there been any localized lesion to be found we feel it would have been in the brain or spinal cord. However, the results of the examination of the trunk are reported as furnished by Dr. J. R. Lisa, Pathologist of City Hospital, because they appear to show that two other hypotheses advanced to explain the condition observed, namely, suprarenal disease and status thymicolymphaticus, are not correct.

Autopsy No. 2510.—L. H., aged forty-three years, died September 25, 1926; autopsy September 28, 1926.

The body was five feet seven inches in height and about one hundred and thirty-five pounds in weight. Rigor mortis was not present. There was nothing

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†Am. Heart Jour., 1925, i, 73.

significant externally. Scrotum contained both testes. After incision, thoracic and abdominal organs were examined in situ; thyroid gland was hypertrophied; there was no evidence of persistent thymus; both adrenals were present and normal in size.

Several large lymph glands adherent to the right bronchus on section were found filled with greenish-yellow caseous material indicative of long-standing tuberculosis.

Lungs: Right three lobes weighed 700 grams; left two lobes, 550 grams. Both were crepitant throughout and showed no areas of consolidation; upon transection there was no evidence of anything abnormal. Pleural surfaces were smooth and glistening throughout.

Heart was markedly dilated on both right and left sides. Muscle wall was thinned out, with evidence of marked fatty degeneration and infiltration. Valve leaflets of both sides showed no evidence of pathology. Pericardium was normal and a normal amount of pericardial fluid was present.

Liver weighed 1350 grams and showed no evidence of abnormality externally or upon transection.

Gall bladder contained one ounce of bile; there were no stones present, ducts were patent and mucous membrane was normal.

Kidneys were small; the right weighed 110 grams, left 150 grams. Fetal lobulations present. Right kidney capsule stripped easily, relation of cortex to medulla, one to three. There was a small hard area one centimeter in diameter in the cortex with two or three similar but smaller areas, probably fibromas.

Spleen weighed 240 grams, had a normal capsule and normal appearance on transection.

Pancreas, stomach, and intestine appeared normal throughout.

Prostate was much smaller than normal, about one inch in diameter and upon section showed marked atrophy.

Bladder was normal and contained 200 c.c. urine.

Histology: Microscopically, the suprarenals were quite normal, as were the other organs with the exception of the bronchial lymph nodes which showed old caseous tuberculosis.

"*Anatomical diagnosis:* Chronic myocarditis, acute dilatation of the heart, atrophy of the prostate, chronic tuberculosis of lymph nodes."

DIRECT EXTENSION OF THROMBUS FROM HEART INTO PULMONARY ARTERIES

L. E. Viko, M.D.
Salt Lake City, Utah

THE unusual extension of a thrombus from the heart into the branches of the pulmonary artery on each side seems to justify reporting the following case.

Mrs. A. B., a widow of fifty-three years, white, entered the L. D. S. Hospital March 17, 1927 complaining of pain in the right knee and shoulder. The family and marital histories disclosed no facts pertinent to the present illness. The past

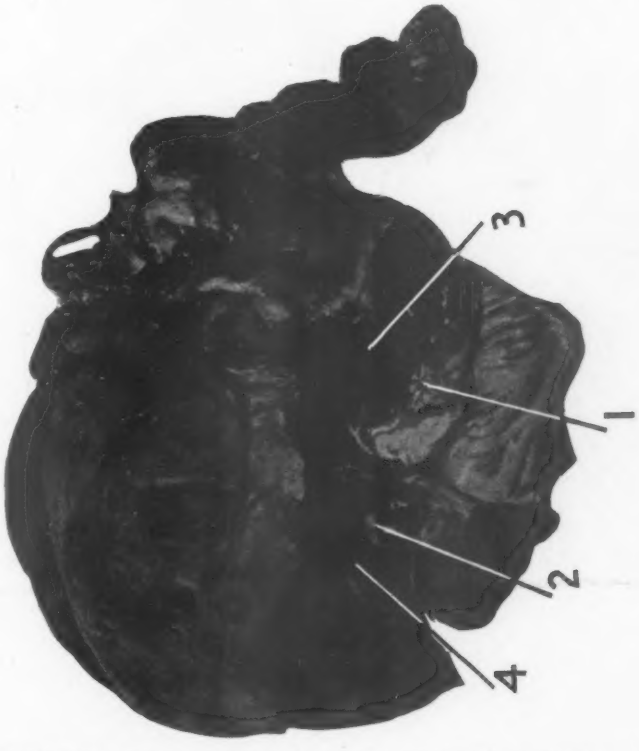

Fig. 1.—Right side of heart opened to show auricle and ventricle. (1) Thrombus in right auricle; (2) thrombus attached to tricuspid valve; (3) recent postmortem thrombus; (4) ventricle.

history was not unusual. For ten years she had had "rheumatism" beginning in the hands and progressively affecting the ankles and knees. She had been able to walk, however, until five days before entrance when the right knee became so painful that she was confined to bed. About this time the right shoulder also became very painful and swollen. The day before entrance she consulted a physician who referred her to the hospital. The temperature was then 101° F. and the pulse rather weak.

Examination at the time of entrance disclosed a woman complaining of great pain in the knee but otherwise not appearing very ill. There was no cyanosis, edema, or obvious dyspnea.

The head and neck showed no abnormality. The lungs were resonant and free from râles. The heart apparently was not enlarged; the rhythm was regular; there was no definite murmur but all sounds were of poor quality. The pulse was poor in volume; the arteries were not sclerotic. The abdomen showed no abnormality. A number of the fingers had the characteristic deformity of arthritis deformans. The right knee and shoulder were swollen, red, and tender. The temperature was 100.2° F. at admission, but dropped that evening to 99.2° F. The

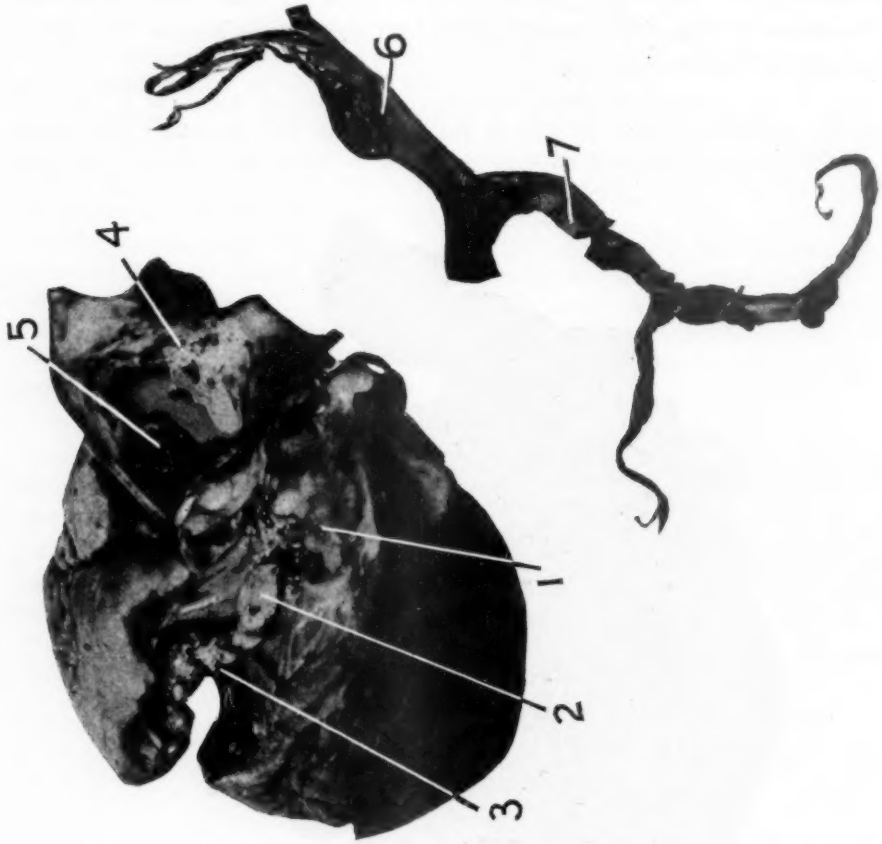

Fig. 2.—Pulmonary artery and aorta opened; also reconstructed thrombus as it extended into pulmonary arteries. (1) Pulmonary artery; (2) thrombus extending from ventricle into pulmonary artery; (3) right ventricle; (4) aorta; (5) thrombus in aorta; (6) and (7) thrombus branching into pulmonary arteries.

pulse was 88, the respiration, 32. The urine showed a trace of albumin and a few hyaline casts and pus cells. The report of an x-ray plate of the right knee was: "general atrophic appearance of the joint; joint space decreased; there is a slight erosion of both sides of the joint—question of tuberculosis."

That night and the following day and night the patient rested fairly well without narcotics. The temperature remained between 98.8° and 99.2° F.; the pulse between 84 and 124 and the respiration was from 20 to 24. At eleven in the morning of March 19 she complained of nausea. At 11:50 A.M. severe pain developed in the right lower chest and upper abdomen. She became cyanotic and markedly dyspneic. Examination shortly after showed no abnormal signs in the lung, but

the general appearance was that of pulmonary embolism. There was some tenderness and rigidity in the right upper abdomen. The heart tones were weak but regular, rate 90; no definite murmur was made out. The pulse was weak. At two in the afternoon the patient was reported somewhat improved. At five in the afternoon she died rather suddenly.

Postmortem examination was made two hours after death. The skull was not opened. There was no abnormality of the abdominal viscera. The right knee joint contained a considerable amount of pus; the cartilages and part of the adjacent bones were eroded; the appearance was that of a purulent arthritis super-

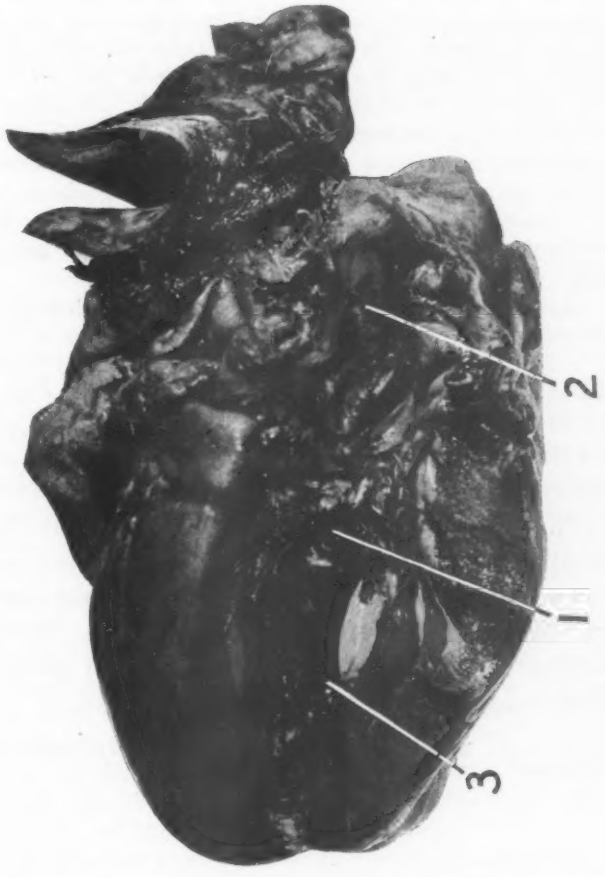

Fig. 3.—Left side of heart opened. (1) Thrombus attached to mitral valve; (2) auricle; (3) ventricle.

imposed upon an old arthritis deformans. The right lung was attached to the parietal pleura in the upper part by several light adhesions. On cutting across the root of the right lung a grey-white thrombus was seen to protrude from each end of the cut pulmonary artery. On opening the branches of the artery in the right lung, the thrombus was found to extend about three centimeters into the main branches of the arterial tree; the lower branch was completely occluded, the upper only partly so. In the part proximal to the heart the thrombus was dense, firm, and greyish-white in color. The part extending into the smaller arteries was softer and reddish-brown in color. The intima of the arteries of the right lung was smooth and glistening and not adherent to the thrombus.

On removal of the left lung, a similar thrombus was found extending into the main branches of the pulmonary artery, and partially occluding the lumen. In several of the smaller arteries the intima was rough and reddened. Over these areas the thrombus was slightly adherent. Neither lung showed any infarcts; both were well filled with air.

The pericardium was normal; the heart showed no marked hypertrophy or dilatation. In the right auricle a thrombus, similar to that described, extended from the auricular appendage (which it filled and to the walls of which it was closely attached) to the tricuspid valve. This thrombus measured about two centimeters in diameter by four and a half in length. Along the right auricular wall it was adherent over a small area. Attached to it on its inner aspect was a more recent thrombus, partly, at least, postmortem in origin. At the tricuspid valve this thrombus was continuous with a verrucous thrombus upon the valve leaflets near their tips partly occluding the valve orifice. From the under surface of the valve a similar flattened thrombus extended into the pulmonary artery. This measured from one to two centimeters in diameter and branched into the artery for each lung. The left auricle was free from thrombi. Attached to the under surface of the mitral valve was a similar thrombus extending about four centimeters into the aorta but not attached to its wall at any point. At its free end it was reddish-brown in color and more friable. None of the valves showed evidence of old endocarditis.

Microscopic appearance of the thrombus from the right auricle and the pulmonary artery was consistent with a thrombus of not more than two or three days duration.

The autopsy findings seem to justify the conclusion that the thrombi were due to an acute bacterial endocarditis secondary to an acute suppurative arthritis, and that the thrombi extended by accretion into each pulmonary artery until occlusion of one or more branches resulted in death. The character of the thrombi and the clinical history seemed to limit the duration of the endocarditis to not more than five days. It was surprising that the fever was so slight and the general condition so little alarming before the day of death. It is unfortunate that the unexpected death prevented more careful clinical study and that no culture was obtained before or after death.

I am indebted to Dr. L. L. Daines for study of the heart and preparation of the microscopic sections.

Department of Reviews and Abstracts

Selected Abstracts

Blumgart, Herrmann L., and Weiss, Soma: Studies on the Velocity of Blood Flow: VI. The Method of Collecting the Active Deposit of Radium and its Preparation for Intravenous Injection. Jour. Clin. Invest., 1927, iv, 389.

The details of a method for collecting the active deposit of radium from radium emanation and its preparation for intravenous injection are described.

The details of a method for breaking several tubes each containing a small amount of radium emanation and the process of transferring the liberated gas to ionization chamber without loss of any of the emanation is described.

A device for automatic registration of the time and duration of intravenous injection is described.

VII. The Pulmonary Circulation Time in Normal Resting Individuals. p. 399.

The method is a further development of the procedure devised for the study of the arm to arm circulation time. The active deposit of radium is injected into the anticubital vein of one arm and its time of arrival is observed first in the right chambers of the heart and later in the arteries about the elbow of the other arm.

The crude pulmonary circulation time in sixty-two measurements on normal resting individuals varied from five to seventeen seconds. The average crude pulmonary circulation time was eleven seconds.

The circulation time of the venous blood from the right elbow to the right auricle varied from two to fourteen seconds with an average of seven seconds.

Repeated measurements in the same individuals showed a maximum variation in the crude pulmonary circulation of three and a half seconds with an average of two seconds while the maximum variation in the venous flow time was seven and a half seconds, with an average of three seconds.

The variations in the velocity of blood flow through the lungs in the same individuals at different times and in different individuals are less than that observed in the velocity of the venous blood of the arm.

No definite relation was observed between velocity of pulmonary blood flow and age of the patient.

With a conspicuous increase in the pulse rate there is a slight but definite increase in the velocity of blood flow through the lungs.

Normal variations in systemic arterial or venous blood pressure bear no relation to normal variations in velocity of blood flow through the lungs.

The average actual pulmonary circulation time observed by the authors was 6.5 seconds; the average minute volume flow through the lungs as observed by others was 6.38 liters. According to the formula $Q = \frac{TV}{60}$ and applying the pulmonary circulation time as mean velocity, T, the amount of blood in the lungs of man averages 589 c.c. or 11 per cent of the total blood volume.

The fact that the proportion of blood in the lungs of man so calculated conforms to that found experimentally in animals indicates that the pulmonary circulation

time is a measure of the mean velocity of blood flow through the lungs and that the available pulmonary pathways are about equal.

Wilson, J. A., and Meek, Walter J.: The Effect of the Pericardium on Cardiac Distention as Determined by the X-ray. Jour. Physiol., 1927, lxxxii, 34.

The authors have studied the restraining effect of the pericardium on the heart in experiments on forty-one dogs.

They have two different procedures in conducting the experiments. First: The chest was opened and the pericardium thoroughly incised to allow complete freedom of the heart. The chest was then reclosed and the size of the heart studied by x-ray pictures taken at different levels of venous pressure. The second procedure was to open the chest, free the pericardiodiaphragmatic attachments and place ligatures in such a position that after the chest had been closed, by drawing the ligatures, the pericardial sack could be opened allowing the heart to contract without any restraining influence.

The results of the experiments have been arranged so as to answer three main questions. First: Is an uncomplicated restraining action of the pericardium always to be found? Second: At what venous pressure levels is such restraint first evidenced? Third: What venous pressure is required to distend the heart to the limits set by the pericardium?

It is shown that not only at high venous pressures but in many experiments it could be shown that the pericardium established a restraining action on the heart at low initial venous pressures. The mechanism by which they assume the diaphragm to influence pericardial restraint on the heart at low venous pressure is by drawing the upper lateral walls of this sack down over the auricles and inhibiting venous filling at these low pressures.

With the pericardiodiaphragmatic attachments severed the uncomplicated restraint exerted by the pericardium on diastolic heart size is first noted at a venous pressure of 0 cm. of water and has reached appreciable magnitude at 2 cm. of water. This restraint increases gradually until the heart fills the pericardium and then becomes more and more apparent the further venous pressure is elevated.

At a venous pressure of about 8 cm. of water or at an effective venous pressure of 15 or 16 cm. of water a dog's heart completely fills the pericardium.

Smith, Fred M.: The Coronary Circulation. Arch. Int. Med., 1927, xl, 281.

The present report is concerned with studies of certain features of coronary circulation in which the author has been interested.

I. The influence of the vagi and sympathetic nerves on the coronary arteries. The question as to whether the vagi and sympathetic nerves provide the coronary arteries with a vasomotor mechanism has been difficult to answer. It is not surprising that the results from the use of epinephrine and electrical stimulation of the nerves have varied because of the difficulty in controlling the various factors which influence the coronary circulation. The contraction of the heart opposes either a dilatation or a constriction of the coronary arteries. The opposition from this factor is conceived to be great in the mammalian heart because of the rapid rate of contraction. This feature is well illustrated by the action of epinephrine on the isolated or intact heart when the dose is sufficient to produce a marked stimulating effect. It is perhaps reduced to the minimum in the slowly beating heart of the tortoise. Even here it was difficult to obtain the constricting effect of epinephrine on the surface vessels after the cardiac rate was accelerated by the stimulating effect of the drug. Furthermore, the blood pressure is perhaps the greatest factor in maintaining the coronary circulation. This has not always been controlled. Then, too, the vagi and the sympathetic nerves are apt not to be clearly separated in the mammal, particularly in the dog, in which the main trunk

of the vagus is said to contain sympathetic fibers. The possibility of stimulating both nerves when intending to stimulate only one cannot be entirely disregarded. At present it would seem that there is no doubt regarding the action of the vagi and sympathetic nerves on the coronary artery of the tortoise. The evidence that these nerves may provide the coronary arteries of the mammal with a similar vasomotor mechanism is suggestive but not conclusive.

II. The Influence of Blood Pressure. The results of experiments show the rate of coronary flow is greatly altered by a change of the diastolic pressure even in the presence of changes in systolic pressure in the opposite direction. Similarly in those experiments in which there was a greater elevation of the diastolic pressure, even though the systolic pressure remained constant or was even slightly reduced there was a comparative increase in the rate of coronary flow. It would seem that the measurements of an efficient coronary circulation is fundamentally dependent upon the height of the diastolic pressure. While the systolic blood pressure no doubt influences the coronary flow, it is subordinate to that of the diastolic pressure.

III. Influence of the Cardiac Rate. The author concludes, from his study, that reduction or acceleration of the cardiac rate within certain limits are associated with definite changes in the rate of coronary flow. The most striking alterations in the coronary circulation were observed during changes from the slow beat induced by vagal stimulation to the accelerated rate produced by warming the sinus node.

IV. The Influence of Cardiac Irregularities. Premature contraction induced by irregular stimulation of the auricles and the ventricles has not produced any significant change in the rate of coronary flow. The effects of auricular fibrillation produced by faradic stimulation of the auricles have varied; in most instances there has been a definite increase in the rate of coronary flow. In one experiment, however, in which the auricular fibrillation appeared spontaneously and lasted for several minutes there was practically no change in the rate of coronary flow after the establishment of a normal cardiac mechanism.

V. The Influence of Caffein and Other Drugs. The variations in the results obtained in investigations of the action of caffein, theobromin, theophilin on the coronary arteries has apparently been due to the difference in the concentration of the drug employed.

Crawford, J. Hamilton, and Rosenberger, H.: Studies on Human Capillaries: IV. Observations on the Nature of the Capillary Pulse in Aortic Insufficiency. Jour. Clin. Invest., 1927, iv, 307, 317.

The caliber of the arterial and the venous limbs of the capillaries in the nail fold has been investigated by means of cinematography in 12 cases of aortic insufficiency in which macroscopic capillary pulsation was present. Simultaneous electrocardiograms were made so that the relation of the capillary changes to the heart beat could be studied.

These studies show that the diameter of the capillaries was constantly changing. Venous capillaries differed in this respect and no two subjects were alike. The blood flow also was very variable. The type of change observed resembled that seen in normal individuals. In several instances the magnitude of the variations in the arterial limb was greater than was seen in normal subjects and in patients with heart disease without cardiac decompensation. The changes in the venous limbs resembled those in normal subjects. The mechanism of the production of these changes is uncertain. No evidence was found of pulsation in the capillaries of the nail fold, although macroscopically pulsation was present.

V. Observations in Cases of Heart Disease with Regular Rhythm.

The caliber of the arterial and venous limbs of the capillaries at the nail fold has been studied by means of cinematography in 8 cases of heart disease with normal rhythm.

The variations which took place in the caliber of the capillaries were of a similar nature to those which had been observed in normal subjects. Those cases which showed no clinical signs of heart failure did not differ in any respect from the normal, while advanced cases showed changes of the same nature but of greater magnitude. They corresponded closely to the changes which were seen in cases of auricular fibrillation with a comparable degree of decompensation. The extent of these variations bore no relation to the pulse rate but seemed to correspond to the state of efficiency of the circulation as judged by the clinical condition of the patient.

The blood flow in the capillaries showed a similar relation to the state of cardiac compensation.

Lambert, R. K., and Rosenthal, A. H.: The Mechanical Efficiency of the Mammalian Heart. Am. Jour. Physiol., 1927, lxxx, 719.

The authors have studied the utilization of energy by the heart by the means of a heart and lung preparation. This heart and lung preparation has been perfused with blood, an analysis being made before and after its passage through the heart alone, for that of the respired gases. Through the use of heparin, it was possible to evolve a preparation demanding the use of but one cat, perfusing the heart and lungs with homogeneous blood. The apparatus used and the details of the method are described.

The oxygen consumption of hearts performing different amounts of work was from 3.3 to 6.7 c.c. per gram per hour.

Attempts to establish a relationship between the factors of work and the oxygen consumption of the various hearts were unsuccessful. It is thought that differences in condition may account for the relative difference in efficiency.

Schmitz, Herbert M., and Preston, Marjorie: Changes in the Carbon Dioxide Combining Capacity of the Blood Following Exercise in Individuals with Organic Heart Disease. Proc. Soc. Exper. Biol. and Med., May, 1927, xxiv, 766.

The subjects used were children ranging from eight to sixteen years, all except two with organic heart disease and all grouped according to the American Heart Association classification. The exercise used consisted in climbing thirty feet of stairs in forty seconds. The first sample of blood was taken after a rest period of one-half hour and again three minutes after exercise was completed. The carbon dioxide capacity was determined by the apparatus of Van Slyke. In the two normal subjects an increase in the carbon dioxide combining capacity was found. In three Group 1 cases, two showed an increase in combining power and one no change. In those described as falling in Group IIA, three showed an increase and four a decrease. Six subjects were classed as IIB, three showing an increase and three a marked decrease. With an increase in amount of exercise, a slight decrease was found in one of the normal individuals; and in the group IIA and IIB cardiacs who previously showed no decrease, a decrease was visible. It is suggested that patients with organic heart disease might be placed in their respective functional groups by determining the effects of exercise on the carbon dioxide combining power of the blood.

Campbell, J. M. H., and Sale, F. J.: Effect of Exercise on Respiratory Exchange in Heart Disease. Arch. Int. Med., 1927, xl, 237.

A detailed investigation of the effect of exercise, roughly equivalent to slow and ordinary walking, has been made in three patients with heart disease. The metabolism relative to the subject's weight did not vary greatly from the normal, which shows that the capacity for increasing ventilation and circulation, rather than any change in the metabolism or total ventilation required, limits exertion. Throughout the range examined, both of these increased regularly with the work done, so that their relationship could be shown graphically by a straight line.

In these patients the extra oxygen intake as the result of work was only slightly higher than normal. As the exercise became harder the percentage of the extra oxygen required, which had to be obtained at the end of the exertion, increased more in the patients. Both these differences would tend to produce breathlessness, but the degree of change would not have been sufficient to do so in a normal subject.

Greater differences were noted in the elimination of carbon dioxide. At the end of exercise it was retained more than normally, so that the output of this gas and the ventilation fell to their resting values more than usual at the beginning and rose considerably more than usual at the end. The percentage of carbon dioxide in the expired air tended to be low, probably because over-ventilation was needed to compensate for defective circulation. In one patient there was practically no rise in the percentage during exercise, so that the whole of the increased output of carbon dioxide had to be obtained by increased ventilation.

The rate and depth of breathing varied in type. In a patient with mitral stenosis it was rapid and shallow. This has been found in several others with mitral stenosis, and is probably associated with the reduced vital capacity and congestion of the lungs to which these patients are liable. The rapid, shallow breathing is itself a further cause of breathlessness. In a patient with aortic disease the breathing was deep and of normal rate. This has been found frequently but not invariably in patients with aortic regurgitation.

Clark-Kennedy, A. E., and Owen, Trevor. The Limitation of Muscular Effort and Its Relation to Cardiac Failure; Quart. Jour. Med., 1927, xx, 383.

The limitation of voluntary effort is usually said to depend on failure of the cardiorespiratory system, more particularly the heart, to effect further oxygen supply to the working muscles. Failure to excrete carbon dioxide seems hardly to have been considered as a possible factor in the determination of the rate of work of which a man is capable.

The symptomatology of extreme muscular exhaustion is not comparable with that of congestive heart failure. Congestive heart failure is characterized by accumulation of blood in the venous system, but this does not occur during severe muscular effort in the normal man. The normal heart is capable of dealing with the venous return of the most intense effort. In heart failure the diseased heart is unable to cope with the venous return under resting conditions.

The respiratory exchange in normal men has been investigated at increasing rates of work over the same period of time breathing (a) air, (b) 26 per cent oxygen, and (c) 16 per cent oxygen at prevailing barometric pressure.

With increasing rate of work (increasing oxygen requirement) the volume of pulmonary ventilation required to effect the intake of unit quantity of oxygen and the excretion of unit quantity of carbon dioxide rises progressively. With increasing rate of work less and less oxygen is taken out of the same volume of inspired air, and less and less carbon dioxide added to it; the alveolar O_2 tension rises, and the alveolar CO_2 tension falls. The percentage of oxygen requirement incurred as debt increases.

During work of the same duration and oxygen requirement, when 26 per cent

oxygen is breathed instead of air, the volume of ventilation required to effect the intake of unit quantity of oxygen and the excretion of unit quantity of carbon dioxide is less. More oxygen is taken out of the inspired air, and more carbon dioxide added to it; the O_2 tension in the alveolar air approximates less closely the O_2 pressure in the inspired air and the alveolar CO_2 tension rises. The percentage of oxygen requirement incurred as debt is smaller.

During work of the same duration and oxygen requirement when 16 per cent oxygen is breathed instead of air, the volume of pulmonary ventilation required to effect the intake of unit quantity of oxygen and the excretion of unit quantity of carbon dioxide is greater. Less oxygen is taken out of the inspired air, and less carbon dioxide added to it; the alveolar O_2 pressure approximates more closely to the pressure of O_2 in the inspired air, and the alveolar CO_2 tension falls. The percentage of oxygen requirement incurred as debt is smaller.

During work of the same duration and oxygen requirement, when 16 per cent oxygen is breathed instead of air, the volume of pulmonary ventilation required to effect the intake of unit quantity of oxygen and the excretion of unit quantity of carbon dioxide is greater. Less oxygen is taken out of the inspired air, and less carbon dioxide added to it; the alveolar O_2 pressure approximates more closely to the pressure of O_2 in the inspired air, and the alveolar CO_2 tension falls. The percentage of oxygen requirement incurred as debt is greater.

The cause of these alterations in the respiratory exchange is discussed. They are attributed to increasing lactic acid acidosis with consequent progressive reduction in the CO_2-carrying power of the blood. The degree of acidosis depends, not only on the rate of work, but also on the composition of the inspired air. At the same rate of work, raising the oxygen pressure in the inspired air decreases, and lowering the oxygen pressure in the inspired air increases, the degree of lactic acid acidosis.

When the rate of work is such that the oxygen supply to the muscles fails, so that lactic acid begins to accumulate, the elimination of carbon dioxide becomes progressively more difficult (a) because the CO_2-carrying power of the blood is reduced, and (b) because more pulmonary ventilation is now required to eliminate the same unit quantity, while more CO_2 must now be eliminated to keep down the rising hydrogen-ion concentration of the blood.

The physicochemical factor in the production of the subjective distress, which limits voluntary effort, is rise of hydrogen-ion concentration of the blood and tissues. During severe muscular exertion the hydrogen-ion concentration rises progressively (a) due to accumulation of lactic acid as the mechanism for oxygen intake fails, and (b) due to the accumulation of carbonic acid as the mechanism for the elimination of carbon dioxide fails. The limitation of voluntary effort is set by the eventual failure of the cardiorespiratory system to prevent rise of hydrogen-ion concentration to the point at which voluntary effort ceases.

The limitation of voluntary effort is determined by the eventual failure of the integrated activity of the cardiorespiratory mechanisms for oxygen intake and carbon dioxide output respectively are so interrelated to each other that, as this point is reached, oxygen supply and carbon dioxide elimination fail together. Moreover during intense exertion the cardiac output of which the heart is capable is still adequate to cope with the venous return.

During extreme muscular exertion *disintegration* of cardiorespiratory function does not supervene. That is to say, one organ does not fail before another, circulation before ventilation; one function does not fail prematurely, oxygen intake before carbon dioxide output; the cardiac output does not fail to keep pace with the venous return.

From the physiological standpoint heart disease is to be looked upon from the point of view of progressive disintegration of function. As the functional efficiency of the heart is reduced by disease, integration of cardiorespiratory function is for

a time maintained by a corresponding reduction in the functional capacity of the mechanical apparatus for breathing. When the limits of this protective reaction are reached, disintegration of cardiorespiratory function begins; circulation now fails before ventilation, oxygen intake before carbon dioxide elimination and cardiac output before venous return. Then alone do the symptoms of congestive cardiac failure supervene.

Katz, Louis N., and Wiggers, Carl J.: The Influence of High Systemic Blood Pressures on the Right Ventricle and Pulmonary Circuit. Am. Jour. Physiol., lxxxii, 91.

On the basis of pressure curves recorded from intact animals, by optical manometers having a high "figure of merit," the authors conclude that the following sequence of dynamic events occurs after mechanical compression of the thoracic aorta:

The small volume of residual blood restrained during the first few systoles following compression causes a slight elevation of initial pressure in the left ventricle, and usually a slight increase in the diastolic pressure level within the left auricle. In the left ventricle this is accompanied by a steeper pressure gradient and a higher pressure maximum.

The increased left auricular pressure has no effect on pulmonary arterial pressures; diastolic pressure in the pulmonary artery remains unaltered as long as the heart rate in the same, and actually falls if it slows.

The greater return of blood through the coronary and other collateral circuits often appears to overbalance somewhat the reduced flow via the inferior vena cava. As a result, right auricular diastolic and right intraventricular initial pressures are ever so slightly augmented. This leads to a slight increase in the isometric gradient of the ventricular contraction, a somewhat higher systolic summit and accounts also for a detectable elevation of pulmonary systolic pressure, often present.

The authors experiments confirm the interpretation of Anrep and Bulatao that changes in pulmonary arterial pressures result from changes in the contraction of right ventricular systole, and are not due to "back pressure effects." The authors' results emphasize the fact, however, that in the intact circulation the changes are so slight that it requires sensitive forms of apparatus to detect their existence. The results obtained from heart-lung preparations can, therefore, not be transferred to the intact animal.

Blalock, Alfred, and Harrison, Tinsley Randolph: The Regulation of Circulation. V. The Effect of Anemia and Hemorrhage on the Cardiac Output of Dogs. Am. Jour. Physiol., 1927, lxxx, 157.

The first study deals with the effects of deficient oxygenation of the blood on the cardiac output. Oxygen deficiency has been produced by the removal of blood and by anoxic anoxemia. Anemia as used in this paper indicates the repeated loss of small quantities of blood over a long period of time, whereas hemorrhage implies the rapid removal of larger quantities of blood. The effects of anemia and hemorrhage on the cardiac output of intact dogs were studied by the Fick method. Diminution of the hemoglobin content of the blood is associated with an increased cardiac output. Progressive hemorrhage leading to decreased blood volume causes no marked change in the cardiac output until the animal approaches the state of shock, when the cardiac output rapidly decreases. When blood volume is maintained by saline infusion, progressive hemorrhage is associated with an increased cardiac output which diminishes as shock sets in.

These effects occur in animals narcotized with morphine and in trained unnarcotized animals. The time element is of considerable importance. The more

rapidly a given degree of anemia is produced the more is the output of the heart increased.

It is suggested that capillary oxygen pressure may be an important factor in the regulation of the output of the heart.

Blalock, Alfred, and Harrison, Tinsley Randolph: The Regulation of Circulation. VI. The Effects of Severe Anoxemia of Short Duration on the Cardiac Output of Morphinized Dogs and Trained Unnarcotized Dogs. Am. Jour. Physiol., 1927, lxxx, 169.

Anoxemia has been produced by rebreathing, the CO_2 being absorbed. The effects of arterial oxygen saturations of 3 to 70 per cent on the cardiac output of morphinized and trained dogs have been studied by the Fick method. Anoxemia of severe degree (greater than 30 per cent unsaturation) causes the following changes: (1) slight increase in pulse; (2) Increased minute ventilation; (3) Diminished oxygen consumption (when the arterial saturation is less than 50 per cent). (4) Uncompensated acid deficit (diminished CO_2 content and decreased P_H). (5) Increase of 5 to 500 per cent in minute cardiac output.

Michailoff, K. P., and Solitermann, M. L.: On the Nature of Extrasystoles. Arch. des Maladies du Coeur., August, 1927, viii, 540.

An analysis of 10 cases of persistent extrasystoles is presented. Atropine injected intravenously caused cessation of the ectopic beats in all but one case, where the patient was refractory to the drug and no symptoms of atropinization occurred. Cases included examples of both organic and functional heart disease, and all types of extrasystoles were included; four of auricular origin, 3 of ventricular origin and 3 cases of the atrioventricular form. The amount of atropine used was fairly large and varied from 1.5 to 3.6 mg. The rate before atropine administration was noted, also the maximum rate occurring after the injection. The difference between the two rates was taken as an indication of the inhibitory power of the vagus and varied in the cases cited from 6 to 57 points. The maximum heart rate following the atropine was taken as a gauge of the tonus of the sympathetic. It is noteworthy that the extrasystoles ceased to occur before the maximum cardiac acceleration and in two cases, while the cardiac rate remained slow. The authors conclude that in all subjects who react to atropine, extrasystoles can always be removed by vagus block. The tonus of the vegetative nervous system is an important factor in the consideration of ectopic rhythms.

Wiggers, Carl J.: The Interpretation of the Intraventricular Pressure Curve on the Basis of Rapidly Summated Fractionate Contractions. Am. Jour. Physiol., 1927, lxxx, 1.

The incidence of intrinsic negativity over different regions of the ventricular surface was recorded by unipolar leads and in conjunction with the pressure curves from the ventricles and aorta. The observation of Lewis and Rothschild that the anterior surface of the ventricles is excited at appreciably different times was confirmed. Roughly speaking, the interpunctual intervals between the base and apex are a little less than 0.02 second. As the interventricular septum and posterior basal aspects of the ventricles are undoubtedly excited, respectively earlier and later, than the anterior surfaces, these values do not express the extreme differences in the excitation of the first and last fractions of ventricular muscle. The intraventricular pressure curve may, therefore, not be regarded as an addition of ultimate contraction in phase but as a summation of rapidly succeeding fractionate contractions.

The intraventricular pressure curve is analyzed on this basis and it is suggested that the early concave rise of pressure is an index of the time required for all frac-

tions to enter into the contracting state. Data are presented which show that, in general, the duration of this phase of entrant contractions varies as the interpunctual intervals. These give the differences in the development of intrinsic negativity of the anterior ventricular surface. Attention is directed to the fact that the incisura of the pressure curve remains our best criterion as to the termination of all fractionate contractions but that previous to this many fractions have progressively ceased their contraction and entered into relaxation. This harmonized with the interpretation of the T-wave of the electrocardiogram which not only begins but reaches its crest or trough long before the end of dynamic systole is reached.

The duration of dynamic systole calculated by standard methods for either ventricle represents very closely the interval which elapses between the inception of the first fractionate contraction to the end of the last fractionate contraction in the ventricle. The fractionate contraction period (i.e., the interval that each unit of ventricular muscle remains in a contracted state) is approximated by the interval from the point of inflection to the incisura.

Wiggers, Carl J.: Are Ventricular Conduction Changes of Importance in the Dynamic of Ventricular Contractions? Am. Jour. Physiol., 1927, lxxx, 12.

There are a priori reasons for believing that variations in the speed with which the fractions of ventricular muscle are excited and summated may affect the gradient, height and duration of the resulting pressure curve. Experiments were carried out to determine to what extent alterations in ventricular conduction do occur when experimental conditions are altered and how far phasic changes in the fractionate contractions rather than fundamental variations in their form determine the dynamic consequences.

Results showed that during circulatory changes produced by increasing the aortic resistance(graded aortic compression), by augmenting the venous return and cardiac filling (saline infusion) and by altering the heart rate do not affect the "interpunctual intervals" of surface negativity even when considerable differences in A-V conductivity occur. Consequently, the general conclusion is reached that changes in ventricular excitation leading to alterations in the phasic summation of fractionate contractions play no role in producing the characteristic effects observed in the intraventricular pressure curves under these experimental conditions.

Changes in gradient, amplitude and duration of ventricular contraction evidenced by the intraventricular pressure curve may, therefore, continue to be regarded as evidence of similar changes in the character of the ultimate contractions as long as the ventricles are excited over normal pathways from a supraventricular focus. This conclusion holds despite the fact that the intraventricular pressure curve represents a rapid serial summation of individual contractions and despite the fact also that the pressure curve developed by each fraction of ventricular muscle probably differs constantly both as to character and contour from that recorded as the intraventricular pressure curve.

Turner, Abby H.: The Adjustment of Heart Rate and Arterial Pressure in Healthy Young Women During Prolonged Standing. Am. Jour. Physiol., 1927, lxxxi, 197.

A system of scoring, based on observations of heart rates and arterial pressures during a prolonged period of quiet standing and control periods of reclining, has been devised which appears to give an index of the ability of the circulation to adapt itself to changes in position.

The results of tests upon twenty-four healthy young women indicate a fair degree of parallelism between the scores by the test and measurement of the circulatory minute volume by the Field-Bock method. The Schneider ratings were

also frequently in agreement, though the new scores spread out more widely and thus serve to differentiate the subjects more clearly. There were some cases of discrepancy.

The heart rate and arterial pressure determinations were tried on a series of forty additional subjects with results which tended to corroborate those of the first series.

The use of the change from reclining to a more or less prolonged period of standing still is suggested for circulatory studies as likely to produce differential results quite as suggestive as those of exercise versus rest. Reasons for this may lie in the essential mechanical difficulties involved in maintaining the erect position and its probable phylogenetic history.

Turner, Abby H.: The Circulatory Minute Volumes of Healthy Young Women in Reclining, Sitting and Standing Positions. Am. Jour. Physiol., 1927, lxxx, 601.

Circulatory minute volumes were determined by the Field-Bock method on twenty-five healthy young women in reclining, sitting and standing positions.

While the metabolism showed as usual a small rise on sitting as compared with reclining and a larger rise on standing, the minute volumes changed in the opposite direction, a fall averaging 10.9 per cent on sitting and 21.2 per cent on standing. The average values in litres for the three positions were, reclining, 6.26 liters; sitting, 5.59 liters; standing, 4.77 liters.

It appeared from a study of the details of the experiments that the difference between the CO_2 of the arterial and venous bloods became greater as standing was continued, a change associated with a fall in the CO_2 of the alveolar air, but that this was too regular and to frequently progressive to be a case of overventilation, a treacherous possibility which was further guarded against by care in technic.

The heart rate was increased in sitting as compared with reclining and further increased on standing. This latter increase was greater than the increase of the metabolism. The output per beat was thus decreased on sitting as compared with reclining and much more decreased on standing.

There are probably relations between circulatory minute volumes and stature, training and season. The essence of the hot weather handicap on the circulation may be the lessened return of blood to the heart due in turn to skin dilatation.

Supporting evidence is offered that such a lessened output from the heart on taking a quiet erect position is in harmony with the ordinary experience of many persons as shown by circulatory embarrassment of various kinds on prolonged and quiet standing. It is further in harmony with the relatively late phylogenetic development of the erect position.

Schneider, Edward C., Clarke, Robert W. and Ring, Gordon C. The Influence of Physical Training on the Basal Respiratory Exchange, Pulse Rate and Arterial Blood Pressure. Am. Jour. Physiol., 1927, lxxxi, 255.

The authors have investigated the relation of basal metabolism to pulse frequency and have followed step by step the basal changes in the gaseous metabolism, pulse rate and arterial blood pressure during a period of regular physical training and during and after a period when no exercise was taken in order to determine how soon and to what extent regular exercise may change each. The observations were made on one athlete and on four men who were ordinarily very irregular in the matter of exercise and who prior to the beginning of the study had led a sedentary life.

The experiments were not planned for the purpose of comparing the athlete and nonathlete, but to find the effect of a period of training on the basal respiratory exchange when any individual indulges in regular physical exercise.

The exercise taken by the subjects resulted in a feeling of well being and in increased alertness. It increased the appetite for food, improved the muscles, and augmented the capacity for doing physical work. Whether it increased the total muscle mass of the body cannot be said. None of the men showed a large change in weight. All of the nonathletes were of the slender type and none had much fat to lose. If there was growth in the size of the muscles during training the authors concluded because of the failure of the basal metabolism to increase in two of the subjects and its decline in the others that the oxygen consumption of the muscles of the body during basal conditions is decreased. It therefore, appears that one of the results of physical training is an increase in the efficiency with which basic life processes are carried on.

During the observations, it was determined that the basal minute-volume of breathing was not clearly altered by the training. Training slowed the basal, and early morning standing posture pulse rates, but did not affect the early morning arterial blood pressure.

Katz, L. N. and Weinman, S. F.: The Relation of the T-Wave to the Asynchronism Between the Ends of Right and Left Ventricular Ejection. Am. Jour. Physiol., 1927, lxxxi, 360.

The time relation of the T-wave to the end of ejection in the left and right ventricle was measured under a variety of experimental conditions. The measurements were made on records of aortic and pulmonary arterial pressure curves registered by optical manometers simultaneously with the standard leads II and III of the electrocardiogram. The curves were projected and transcribed on coordinate paper for measurement.

No parallelism existed between the asynchronism of the termination of ejection in the two ventricles and the character of the T-wave under control conditions.

No consistent relation was found between the changes in the T-wave and the variations in asynchronism of the end of right and left ejection when the circulatory conditions were altered. The T-wave, on several occasions, became inverted without any accompanying change in this asynchronism.

The time relation of the T-wave to the end of the two ejections varied considerably from animal to animal and in the same animal when conditions were altered. No better correlation could be made with the end of right ejection than with the left.

A qualitative parallelism was found between the changes in asynchronism and the T-wave when ventricular extrasystoles were induced. When correlated with the recent tendencies in the interpretation of electrical variations, the results indicate that the T-wave is not due to a persistence of activity on one ventricle or another, nor to persistence at the apex, or base, nor dependent on the pathway of invasion, but rather to the non-uniform duration of activity in the various fractions of the ventricles.

The electrocardiogram is in reality the first differential quotient (comparable to a tachygram) expressing the changes in the algebraic sum of electrical stresses in the heart from moment to moment, oriented in the direction of the lead. On this basis the T-wave is the evidence of unstable electrical stress at the end of activity, produced by the nonsynchronous cessation of electrical activity in all fractions of the heart.

The end point of ejection selected, namely; the beginning of the incisura in the arterial pressure curves, indicates the moment in each ventricle when the ventricle, as a unit, ceases to contract and begins to relax. It does not mark the cessation of all activity, some fibers having begun to relax before this period, and others continuing to contract after this time. The inconsistent relationship between the T-wave and asynchronism of the end of right and left ejection is explained on this basis.

Heinbecker, Peter: The Mechanism of the Respiratory Waves in Systemic Arterial Blood Pressure. Am. Jour. Physiol., 1927, lxxxi, 170.

The author has investigated the character of the respiratory waves in systemic blood pressure, using a method permitting the simultaneous recording of systolic and diastolic blood pressure changes. The work is divided in two parts. Part one was carried out on five men with no known physical anomalies. As a result of this study, the author concludes that in normal respiration there is invariably an immediate diminution in the amplitude of the subsystolic pulse wave on inspiration, an immediate increase in amplitude on expiration. The subdiastolic pulse wave showed an immediate increase in amplitude on inspiration and an immediate decrease in amplitude on expiration. When the durations of inspiration and expiration were within the normal limits these changes lasted throughout the particular phase of the respiratory act.

The second part consists of an experimental investigation of the changes in blood flow and vascular bed capacity occurring in the lungs during respiration.

Analysis of the observations shows that when the negative pressure is employed there is during the actual period of inflation an increased flow into the lungs with a diminution in the outflow. After inflation has been completed the outflow increases at a rate corresponding to the continued but now constantly increased inflow. The inflated lung accommodates more blood than the deflated lung and offers less resistance to the flow of blood.

With positive pressure the opposite conditions hold.

de Boer, S.: Nature and Origin of Accumulated Extrasystoles and Isolated Extrasystoles. Arch. des Maladies du Coeur, May, 1927, 281.

The author discusses the theories of circus contraction and of parasystole in the production of accumulated and isolated extrasystoles. The experimental production of extrasystoles of ventricular origin shows that the excitation wave spreads not only over the ventricles but along the A-V bundle to the auricle and sinus where it may meet the following normal sinus impulse. Only in those extrasystoles produced towards the end of the pause does the following sinus impulse reach the refractory ventricle. Auricular systoles produced by two such impulses travelling in opposite directions could arise chiefly from one or might be a product of both equally. In the latter case the impulses would necessarily meet in the middle of the auricle and as no difference in potential would be present, no P-wave need be produced.

An induction shock, applied to the A-V bundle, may produce two extrasystoles. The author assumes that both auricles and ventricles are stimulated and that the auricular impulse then travels through the A-V bundle towards the ventricle, producing a further extrasystole.

Paroxysmal tachycardia was produced experimentally in exsanguinated frogs by an induction shock applied to the ventricle immediately after the refractory phase. The explanation of this condition lies in the poor metabolic condition of the muscle when the excitation wave travels slowly and in one direction. He considers that paroxysmal tachycardia differs from fibrillation in that the excitation wave in the latter travels irregularly. An auricular form of paroxysmal tachycardia was similarly produced. Inequality of the auricular contractions could be explained by the impulse travelling through different parts of the auricular muscle. A ventricular contraction may follow each auricular beat or only the second or third. Auricular flutter is similarly explained.

An auriculoventricular form of paroxysmal tachycardia was produced by stimulating the A-V bundle. Two types of response are recorded: in the first an auricular contraction occurred after every second ventricular beat, in other words, the impulse traversed auricle, ventricle, bulb, ventricle, auricle, in that order. The

other type showed an equal number of auricular and ventricular contractions and several explanations are given for this occurrence.

The author points out that in man paroxysmal tachycardia can be similarly explained. The occurrence of a bundle of His instead of the auriculoventricular band makes the A-V form more difficult of explanation. He considers that a second connecting band (described by Stanley Kent) may be present. This could presumably carry impulses in a direction opposite to that of the bundle of His and might be present only in those persons subject to the A-V form of the condition. Secondly, one could presume a functional dissociation in the bundle of His so that impulses could travel in opposite directions in different parts of the bundle.

The transition from fibrillation to flutter under experimental conditions may be direct or indirect. In the direct transition some metabolic improvement takes place in the muscle and the wave can travel without halting. The rate is slowed and fibrillation is changed to flutter. Indirect change from ventricular fibrillation is effected when the retrograde impulses from the ventricle produce multiple auricular extrasystoles. After the ventricular fibrillation ceases, the auricular systoles are followed by ventricular contractions at a more rapid rate. The author was successful in producing experimental cessation of circus movement by applying a second shock in the same place as the first. The excitation wave finding the path refractory travels in the opposite direction and meets the first impulse. The abnormal rhythm then changes to the normal mechanism. The author describes a form of extrasystole distinguished from the usual type by its occurrence early in diastole. Here the impulse apparently travels again over the same circuit as the normal systole. To this form, he gives the name of satellite systole.

Parasystole as a mechanism in the production of extrasystole is criticized. As true examples of parasystole are rare, the author does not believe they can serve as a basis for a theory for multiple extrasystoles. He discusses the cases quoted by Kaufmann and Rothberger as instances rather of circus movement than of parasystole and shows that Gallavardin's instances of five coupled beats in a case of complete arrhythmia was an example of satellite systoles and due to re-entry.

Seegal, David, and Seegal, Beatrice Carrier: Studies in the Epidemiology of Rheumatic Fever. Jour. Am. Med. Assn., 1927, lxxxix, 11.

The authors, by means of a questionnaire sent out to selected hospitals in this country, have compiled statistics showing the incidence and seasonal occurrence of rheumatic fever. The figures for the final two years of the study 1924 and 1925 demonstrate an increased rate of rheumatic fever in some of the hospitals of the series.

Hatcher, Robert A., and Weiss, Soma: Reflex Vomiting from the Heart. Jour. Am. Med. Assn., 1927, lxxxix, 429.

Experiments on intact and eviscerated animals show that the emetic action of the digitalis bodies is not exerted on the stomach or intestine.

Vomiting is not induced by the direct application of any digitalis body directly to the center, though it has been induced in this way with minute amounts of many drugs.

Vomiting is not induced by the perfusion of the brain with blood to which a digitalis body has been added, but it is induced by the intravenous injection while the brain is perfused with blood in such a way as to exclude the digitalis body from the center.

Cutting the cardiac fibers of the vagi and extirpation of the stellate ganglions, or cutting the cord above the level at which fibers from the heart enter, abolishes the emetic action of the digitalis bodies. The effect is not due to depression, as has been intimated, for the far more severe operation for evisceration does not inter-

fere with the emetic action of these drugs. New paths are probably formed after the heart has been denervated so far as possible.

Nicotine abolishes the emetic action of ouabain and that of intravenous doses of strophanthidin and mercuric chloride, when they are applied directly to the peritoneum. It does not depress the vomiting center.

The vomiting center is not stimulated for more than a few minutes by the direct application to it of a single dose of any emetic so far as we know. Recovery follows promptly after the application of a moderate dose, and depression follows a large dose within a short time. The cardiac actions of digitoxin and those of digitalis are persistent, and their emetic action often persists for days. The cardiac action of strophanthidin is brief; and its emetic action is correspondingly fleeting. A similar correspondence exists between the duration of the cardiac action, and that of the emetic action of other digitalis bodies.

Evidence that the heart is provided with the nervous mechanism for reflex vomiting is also afforded by the fact that nausea and vomiting (with belching) are common symptoms attending coronary occlusion and angina pectoris.

The only published work that seemed to afford evidence that the digitalis bodies induce vomiting otherwise than through their action on the heart actually supports the view expressed here, because larger intraperitoneal doses of the digitalis body used were necessary to cause vomiting after the cardiac nerves had been cut than were required in the intact animal. The emetic action is then exerted locally on the peritoneum.

The authors were unable to devise any single type of experiment which would afford absolute proof that the digitalis bodies induce vomiting by their action on the heart, but the evidence of some 200 experiments of many kinds points to the heart as the seat of this action; this, together with the fact that evidence to the contrary has not been obtained, affords the strongest proof that the digitalis bodies induce vomiting reflexly by their direct action on the heart.

Levy, Robert L., and Mackie, Thomas T.: The Drug Treatment of Heart Disease. Jour. Am. Med. Assn., 1927, lxxxix, 432.

The authors discuss various important drugs that have been employed in the treatment of circulatory disturbances. These drugs considered are digitalis, quinidine, diuretics and sedatives.

In addition brief discussion is made of miscellaneous drugs such as nitrites, salicylates, barium chloride, and those drugs used in the treatment of cardiovascular syphilis.

Hartman, F. W., Bolliger, Adolph, Doub, F. P., and Smith, F. Janney: Heart Lesions Produced by the Deep X-ray. Bull. Johns Hopkins Hosp., 1927, xli, 36.

The authors have studied the myocardium in three patients who had died in the hospital. The patients had had malignant diseases of the media stinum and had received considerable amounts of x-ray treatment.

Sections of the myocardium from these patients showed changes comparable to those found in experimental animals following exposure to x-ray.

They have also studied the effects of carefully measured irradiation upon the heart of the experimental animal, sheep or dog. If the dosage is sufficient either in a single massive or in often repeated smaller applications certain characteristic pathological changes are brought about in the heart.

The gross changes are as follows: (a) Hydropericardium. (b) Hemorrhagic infiltration of the right auricle, especially of the right auricular appendage. (c) More rarely, after heavy dosage has been projected through the side, there is thickening and hyaline degeneration of the epicardium with hemorrhagic infiltration of the ventricular walls. (d) At autopsy these animals show passive congestion of the viscera.

Certain characteristic microscopical changes in the heart have been described: (a) in the auricular myocardium, (b) in the ventricular myocardium, (c) in the His bundle of the sheep.

These microscopic myocardial changes vary with the acuteness or chronicity of the lesions produced.

Electrocardiographic records made from the different dogs used in the experiments reported showed a variety of deviations from the normal, more noteworthy changes being: (a) Inversion of T in leads I and II and frequently in III as well. Certain abnormal forms of T. (b) Paroxysmal tachycardia. (c) Auricular flutter was recorded in four animals. (d) Auricular flutter was recorded once. (e) Slight prolongation of the P-R interval. (f) Diminished QRS voltage.

Eyster, J. A. E.: Venous Pressure in Cardiac Decompensation. Jour. Am. Med. Assn., 1927, lxxxix, 428.

The conception that the heart responds to an increased load with increased work has greatly extended the understanding of the behavior of the heart in cardiac disease and in heart failure.

Cardiac decompensation occurs when the initial load on the ventricles represented by the venous pressure, exceeds the physiological limit of the muscle to respond to an increased load by increased work. The muscle stretches beyond its physiological limits, and the contractions are weak and inefficient. An acute dilatation supervenes, as has been shown by the usual methods of physical examination and the more exact methods of roentgen-ray study. This may conceivably occur as the result of a reduced range of physiological response on the part of the muscle or an abnormally high venous pressure load, or both of these factors acting together. The primary factor is doubtless a narrowed range of response of the muscle due to disease.

A subsequent increase of initial load may exceed this range and acute dilatation and decompensation supervene. When this occurs the heart fails to move the load effectively and a further increase of venous stagnation and rise of venous pressure results, which increases to a greater degree the margin between the extent of the load and the upper limit of physiological response on the part of the muscle. The vicious circle of cardiac decompensation thus becomes established. Under these conditions the venous pressure, even under condition of rest, is abnormally high and varies directly with the intensity of the failure.

The most effective guide and index in the rational treatment of cardiac decompensation is the systemic venous pressure. The most immediately effective method of lowering the venous load is the direct removal of blood from the systemic veins. The author has studied the effect of venesection in twenty-one cases of severe decompensation, ten of these being instances of primary endocarditis; in sixteen, previous periods of cardiac decompensation had occurred. The lowest venous pressure before venesection was 15, the highest 36 centimeters of water. In all but one the venous pressure was 20 cm. of water or higher. The average for all cases was 23 cm. The amount of blood removed varied from 265 to 600 c.c. The lowest venous pressure level obtained within forty-eight hours following venesection was 12 cm. of water. Immediate clinical improvement was noted in fifteen cases. In six of these the venous pressure remained low and compensation was restored. Of the nine patients in this group who died in the hospital the termination in four was by what may be called circulatory accidents. In the recoveries, the fall of venous pressure subsequent to the venesection was maintained. In six cases clinical improvement did not result, the fall of venous pressure was not maintained and death occurred within thirty-six hours in five, and on the twentieth day in one.

Leriche, Rene, and Fontaine, Rene: Four Cases of Angina Pectoris Treated Surgically. Arch. des Maladies du Coeur, August, 1927, viii, 34.

The authors report in detail four cases of angina pectoris treated by cervical sympathectomy.

The first case, a man of fifty-one years, had suffered from typical angina for three or four years. Physical findings included a mild hypertension and slight dilatation of the aortic arch. Under local anesthesia the left superior cervical sympathetic ganglion was removed, also the trunk of the nerve as far as the stellate ganglion and the communicating branches of the vertebral nerve and of the inferior cervical sympathetic ganglion were cut. Following the operation the phenomenon of Claude Bernard-Horner was present in this and also in the other cases reported. Recovery was uninterrupted and two years later the general health was improved and no further attacks had occurred.

A second case recorded, a woman thirty-four years old, had a history of angina of twelve years' duration. The attacks were precipitated with effort, fatigue, emotion and occasionally occurred without obvious cause and during sleep. The attacks were becoming more severe, were typical of angina pectoris and were followed by headache, and syncope. Examination showed slight aortic dilatation and the Wassermann reaction on the spinal fluid was positive and medical treatment did not influence attacks. Under local anesthesia the superior cervical sympathetic ganglion was severed from its branches. During the operation tension was applied to the inferior cervical sympathetic ganglion and a typical anginal attack occurred, which was promptly stopped by the injection of novocaine into the ganglion. The patient improved but the attacks recurred the following year. The field of operation was reopened and the superior cervical sympathetic ganglion removed along with cicatrized tissue. Complete relief followed.

The third patient was a man, aged sixty, with a history of angina pectoris, increasing in severity over seven years and latterly accompanied by signs of cardiac failure. Intensive medical treatment was of no avail. Examination showed aortic dilatation and hypertrophy of the left ventricle. The electrocardiogram showed a complete arrhythmia with flattening of the T-wave. The Wassermann was negative and no hypertension was present. The sympathetic trunk was cut at the upper border of the stellate ganglion. All communicating branches were severed and the ganglion was freed from all its attachments except to the thoracic chain. The cardiac arrhythmia disappeared and complete relief followed for nine months, at which time the patient died suddenly with a return of the total arrhythmia.

The last case recorded was that of a man of fifty-six years, whose father had died of angina pectoris. Cervical sympathectomy was performed six weeks after the onset of typical symptoms, which had not responded to medical treatment. Cardiac enlargement associated with aortic insufficiency and without hypertension was present. Operation consisted of removal of the superior cervical sympathetic ganglion and section of the anterior sympathetic trunk. The electrocardiogram which was normal before operation subsequently showed changes in the T-wave. Some improvement followed, but death occurred suddenly six months later.